

Pages 1-178 and 198-220 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

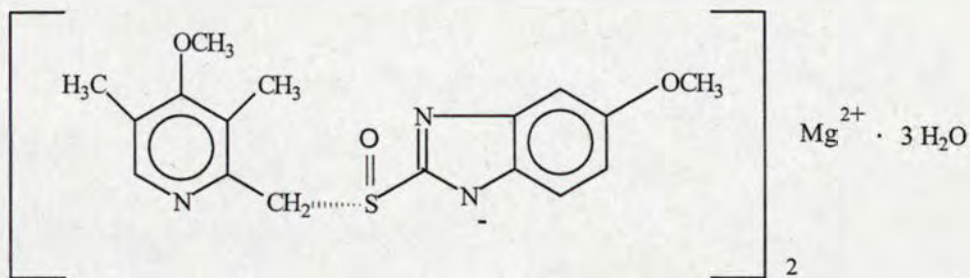
NEXIUM®
(esomeprazole magnesium trihydrate)
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE DRUG

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS Number: 217087-09-7
Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$
Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methylacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres. The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red C177491. In the 20 mg tablet iron oxide yellow C177492 is also added.

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1. % GORD patients with intragastric pH > 4 for at least 8, 12 and 16 hours

Population	Study drug	% GORD patients with intragastric pH > 4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2. Time and % patients with intragastric pH > 4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH > 4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

*p < 0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH>4	% Patients with Intragastric pH>4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see Clinical Trials).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical Trials and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric-coated pellets in tablets. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Clinical Trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=11,950) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^Ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg or lansoprazole 30 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 4).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 4).

Table 4. Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654) 8 wks 87.6% (n=654)	4 wks 66.5% (n=656) 8 wks 83.8% (n=656)	4 wks 61.4% (n=650) 8 wks 81.4% (n=650)
B3	- -	4 wks 66.4% (n=587) 8 wks 86.5% (n=587)	4 wks 65.6% (n=588) 8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

^Ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

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35**Maintenance treatment of erosive reflux oesophagitis**

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6-month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; H. pylori status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 5). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6 % of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 5 Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.

Statistic	NEN-0001	NEN-0003
	E20 vrs placebo	E20 vrs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

*a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n = 440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p= 0.023) and Week 8 (E40 p = <0.001, E20 p = 0.003) compared to the ranitidine 150mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p = 0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40mg and esomeprazole 20mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

***Helicobacter pylori* eradication**

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxycillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxycillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively.

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (eg. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see INTERACTIONS WITH OTHER DRUGS).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Special patient populations

CYP2C19 enzyme

Approximately 3 % of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30 % higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

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29**Carcinogenesis, mutagenesis, impairment of fertility**

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure.

Use in Pregnancy Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in Lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast-feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER DRUGS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole*Demonstrated interactions*Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Theoretical interactions

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP 3A4 other than clarithromycin (eg. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Effects of esomeprazole on other drugs*Demonstrated interactions*Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Atazanavir

Concomitant administration of esomeprazole may reduce the plasma levels of atazanavir.

Theoretical interactions

Ketoconazole or itraconazole

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

ADVERSE REACTIONS

NEXIUM is well tolerated. Adverse reactions are provided for esomeprazole (see **Clinical trials and post-marketing data**) and for the racemate, omeprazole independent of the dose (see **Post-marketing data for the racemate(omeprazole)**), consistent with the pharmacology and clinical use of these pharmaceuticals. Most adverse reactions reported with omeprazole have been mild and transient and there has been no consistent relationship with treatment.

Clinical trials and post-marketing data

The following adverse reactions (see also Table 6) have been identified or suspected in the clinical trials programme for esomeprazole and/or from post marketing use. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal:

Common: diarrhoea, flatulence, abdominal pain, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders

Rare: malaise, hyperhidrosis

Table 6. Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)

	E Total N=519	E 40 N=173	E 20 N=179	E 10 N=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Post-marketing data for the racemate (omeprazole)

The following adverse drug reactions have been observed for the racemate (omeprazole) and may occur with esomeprazole.

Gastrointestinal

Very rare dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Other	
Rare	fever
Very rare	impaired renal function, including nephrosis, dyspnoea, weight increase and hypokalaemia (reported in children)
Endocrine	
Very rare	impotence (although causality has not been established)

DOSAGE AND ADMINISTRATION

NEXIUM should be swallowed whole with liquid. The tablets should not be chewed or crushed.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Gastro-Oesophageal Reflux Disease (GORD)

- Treatment of erosive reflux oesophagitis
40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

- Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse
20 mg once daily
- Symptomatic treatment of gastro-oesophageal reflux disease (GORD)
In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

- Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy
20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.
- Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

- Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk
20 mg once daily. Controlled studies did not extend beyond 6 months.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxycillin and 500 mg clarithromycin, both twice daily for 7 days.

Use in Children

NEXIUM should not be used in children since no data is available.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

PRESENTATION

NEXIUM 20 mg are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A / EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A / EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Storage

NEXIUM 20 mg and 40 mg: stored below 25°C. Available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

POISON SCHEDULE

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

Trade Marks herein are the property of the AstraZeneca Group

Date of TGA approval 27 June 2005

Date of most recent safety related notification 19 May 2006

Pages 1-119 and 146-220 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

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NEXIUM[®]

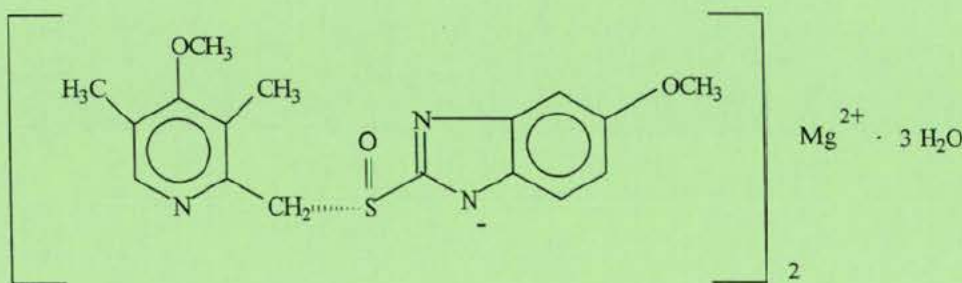
esomeprazole magnesium trihydrate
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg \cdot 3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methylacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres. The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red C177491. In the 20 mg tablet iron oxide yellow C177492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of

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granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres.

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

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In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

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Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

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Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and

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increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

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(grades A to D, according to the Los Angeles endoscopic classification system^v) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The

^v The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

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proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose ($p=0.0006$) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose ($p=0.018$) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials ($n=750$) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

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In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Q2

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 43 (93.3%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

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GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

Statistic	NEN-0001	NEN-0003
	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important



Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 $n=406$; SH-NEN-0006 $n=440$); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population ($n=399$) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 $p=0.036$, E20 $p=0.023$) and Week 8 (E40 $p<0.001$, E20 $p=0.003$) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population ($n=301$) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population ($n=410$) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 $p=0.009$, E20 $p=0.003$). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

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A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis

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or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single center study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

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Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C _{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t _{max} (h)	2.00	1.75	1.6	1.6
t _{1/2} (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and t_{1/2}, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C _{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12

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months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol}\cdot\text{h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol}\cdot\text{h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_{τ} , AUC_{0-24} , and C_{ssmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH} > 4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were

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observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

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Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Demonstrated interactions

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Theoretical interactions

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Effects of esomeprazole on other drugs

Demonstrated interactions

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

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NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Atazanavir

Concomitant administration of esomeprazole may reduce the plasma levels of atazanavir.

Theoretical interactions

Ketoconazole or itraconazole

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Potential interactions that have been excluded

Amoxycillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

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Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

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Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

30/9/07

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DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

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Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxycillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

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PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval:

NEXIUM is a trade mark of the AstraZeneca group of companies.

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2014/8

Pages 1-223 and 252-253 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

Product Information

Clean Version

NEXIUM®

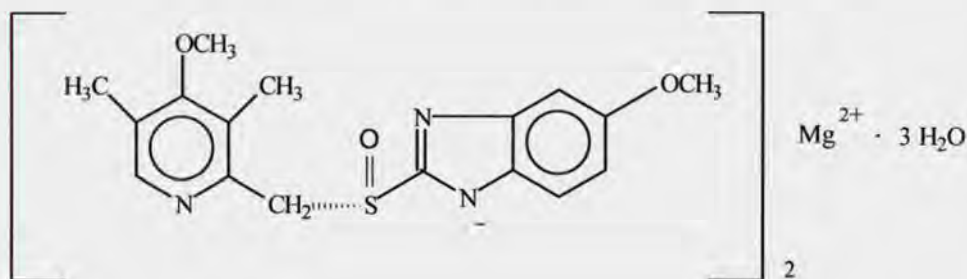
esomeprazole magnesium trihydrate
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg \cdot 3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres. The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of

granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres.

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

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In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

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Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with

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peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

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CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system[¶]) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

[¶] The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

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Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

Statistic	NEN-0001	NEN-0003
	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009,

E20 $p=0.003$). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 $n=585$; SH-NEN-0014 $n=844$); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial ($n=992$) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*

- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single center study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol}\cdot\text{h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol}\cdot\text{h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_t was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_τ , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH > 4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2 -receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 $\mu\text{mol}/\text{kg}\cdot\text{day}$, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were

most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Demonstrated interactions

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Theoretical interactions

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Effects of esomeprazole on other drugs

Demonstrated interactions

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a

31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and antiretroviral drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar

pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as atazanavir and nelfinavir is not recommended.

Theoretical interactions

Ketoconazole or itraconazole

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Potential interactions that have been excluded

Amoxycillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For

a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 30 April 2008

Date of Most Recent Amendment: 7 April 2009

NEXIUM is a trade mark of the AstraZeneca group of companies.

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Pages 1-134 and 163-253 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

NEXIUM®

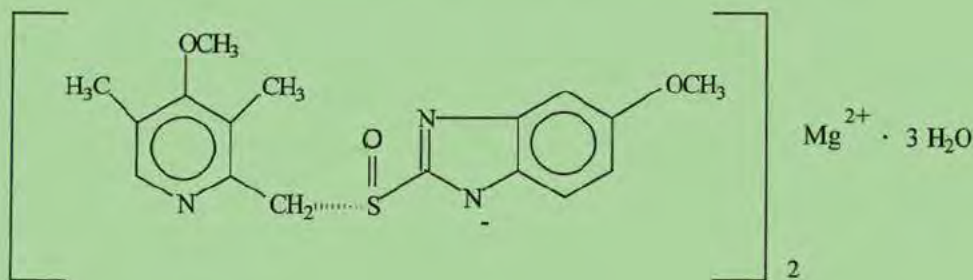
esomeprazole magnesium trihydrate
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg \cdot 3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres. The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of

granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres.

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric	% patients with intragastric pH >4 for at least:		
		pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and

increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

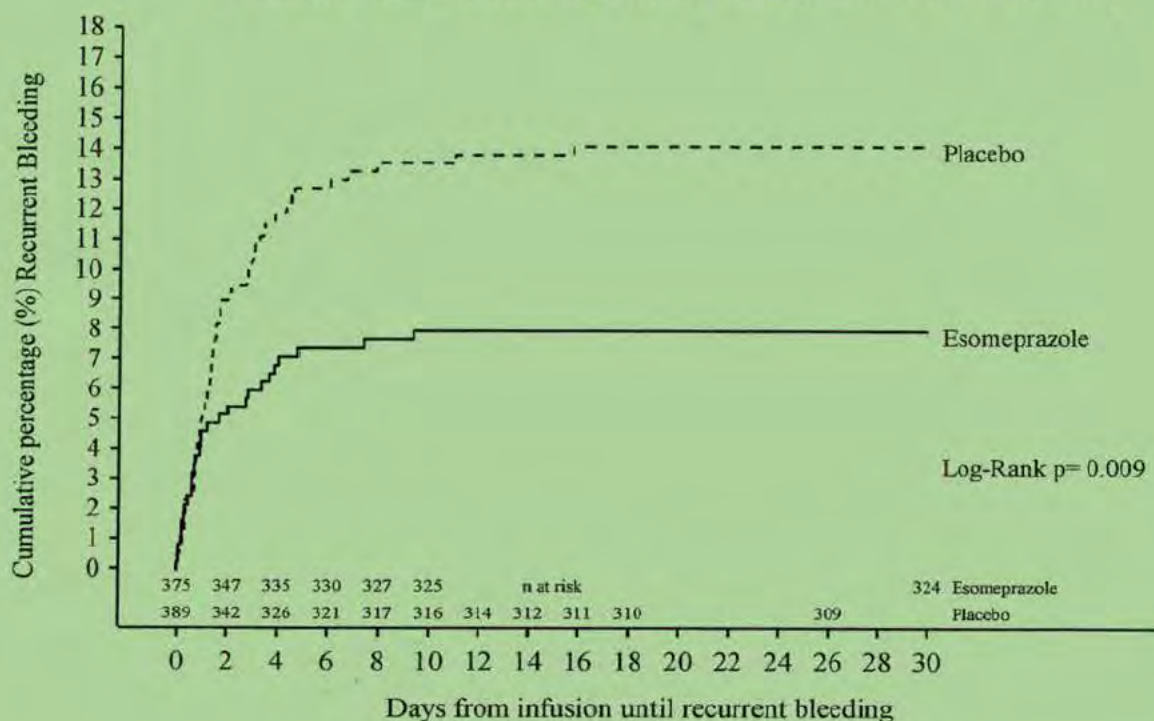
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day

treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanivir (refer Effects of esomeprazole on other drugs)

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_{τ} , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2 -receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 $\mu\text{mol}/\text{kg}\cdot\text{day}$, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were

most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated. Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For

a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: TBC

NEXIUM is a trade mark of the AstraZeneca group of companies.

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Pages 1-99 and 128-253 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

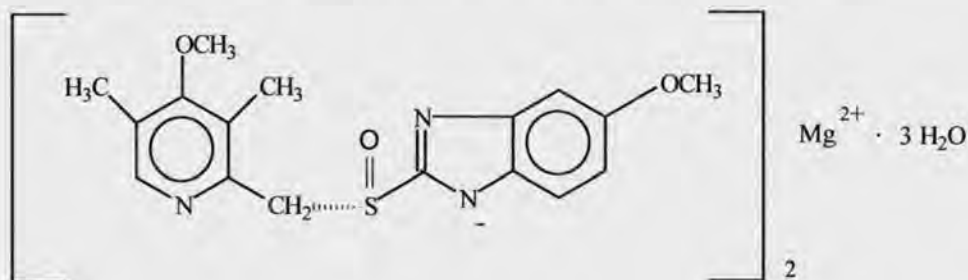
NEXIUM®
esomeprazole magnesium trihydrate
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

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Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

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Table 3

Population	Study Drug	Mean Time Intra gastric pH >4	% Patients with Intra gastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intra gastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intra gastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intra gastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

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(grades A to D, according to the Los Angeles endoscopic classification system¹⁴⁷) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The

¹⁴⁷ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

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proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

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In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

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Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

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A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

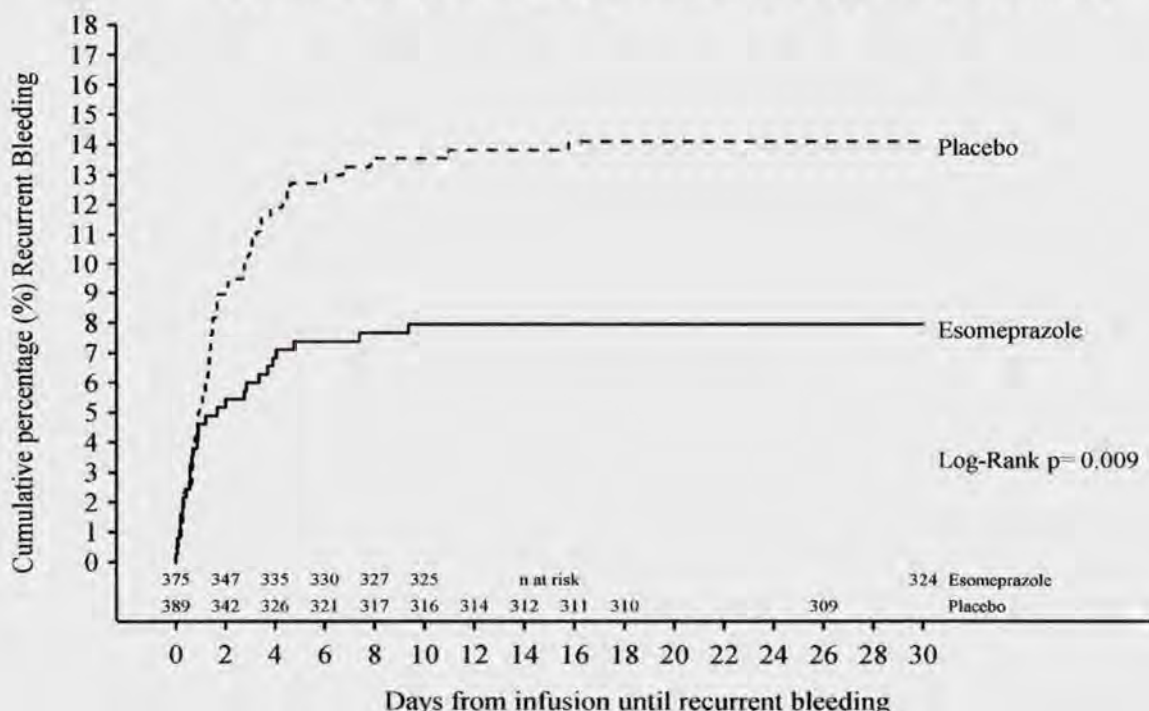
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

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Figure 1 Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day

treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

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CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol}\cdot\text{h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max} .

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

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Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_t was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{∞} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

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Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2 -receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 $\mu\text{mol/kg.day}$, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

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Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

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Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure

appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

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Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

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PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 7 September 2009

Date of most recent amendment: 25 September 2009

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Pages 1-200 and 216-253 have been removed in accordance with section 22 of the FOI Act on the basis that they are out of scope of the request.

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Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with

peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

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CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

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Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

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Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

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In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, ~~43~~ 40 (93.388.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of "time to study discontinuation due to unwillingness to continue" there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

LS

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

Statistic	NEN-0001	NEN-0003
	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009,

E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, p=0.0007, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

W3

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*

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- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single center study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73

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	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_t was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH > 4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

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Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2 -receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 $\mu\text{mol}/\text{kg}\cdot\text{day}$, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were

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most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Demonstrated interactions

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Theoretical interactions

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Effects of esomeprazole on other drugs

Demonstrated interactions

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a

NEXIUM®

esomeprazole magnesium trihydrate

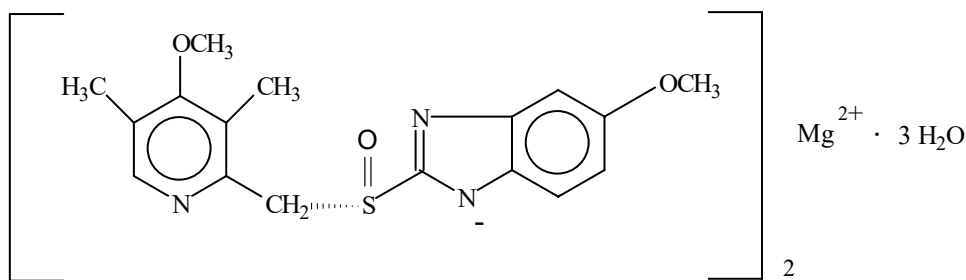
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red C177491. In the 20 mg tablet iron oxide yellow C177492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as

^ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

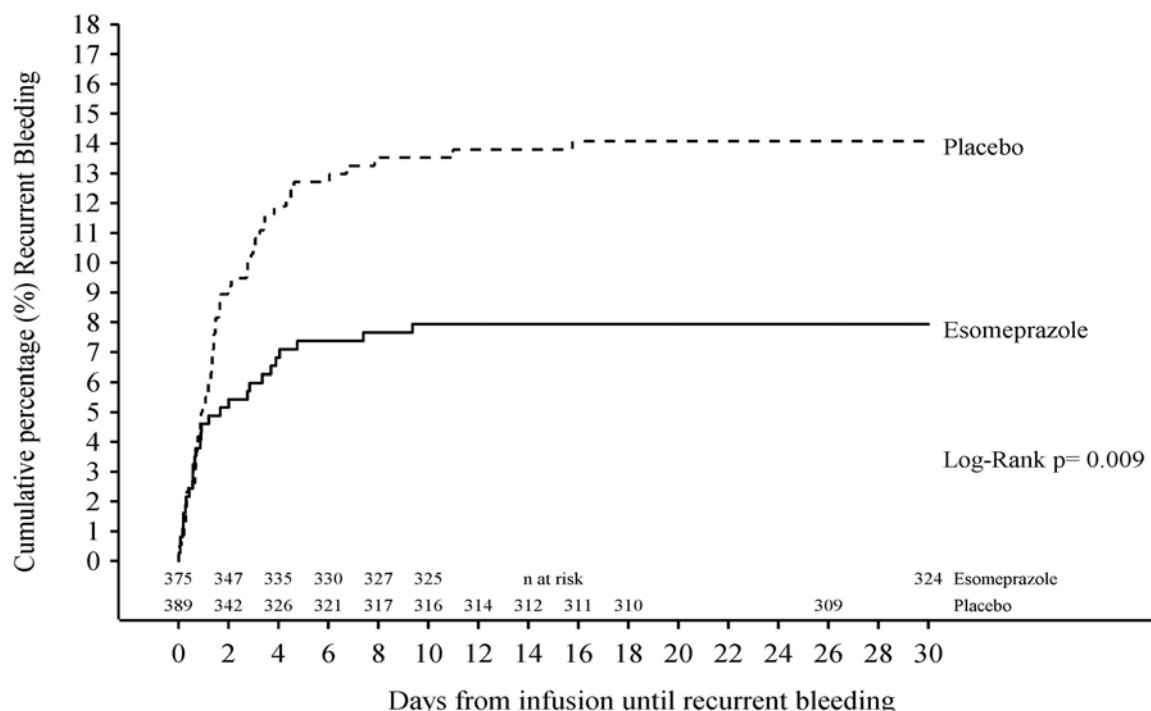
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day

treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C _{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_τ, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease and the absorption of digoxin can increase during treatment with esomeprazole.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$

and <1%; rare $\geq 0.01\%$ and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 7 September 2009

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NEXIUM®

esomeprazole magnesium trihydrate

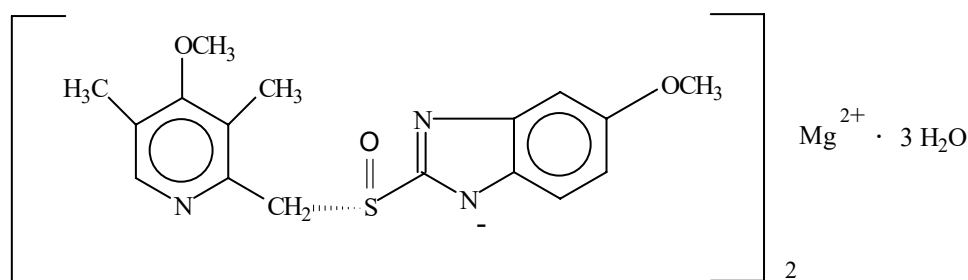
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red C177491. In the 20 mg tablet iron oxide yellow C177492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as

^ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

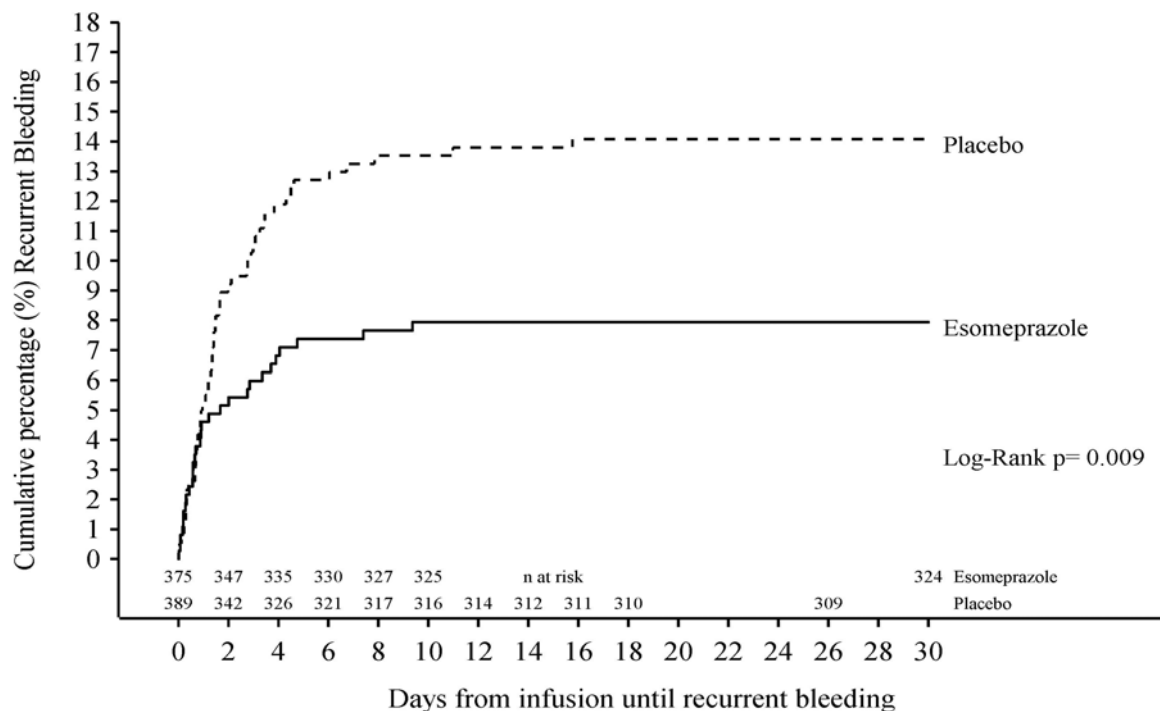
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day

treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C _{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_τ, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

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Alma Road
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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 22 December 2010

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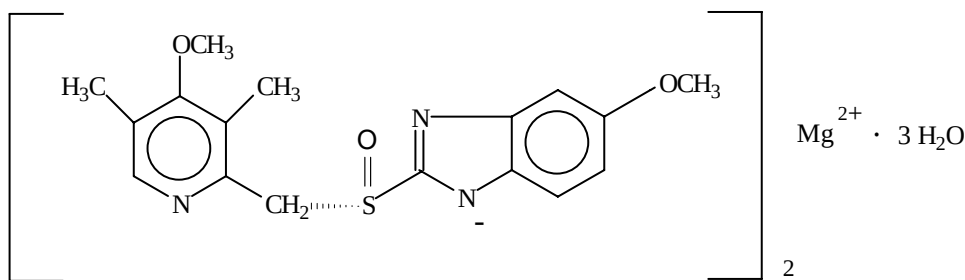
NEXIUM®
esomeprazole magnesium trihydrate
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg \cdot 3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red C177491. In the 20 mg tablet iron oxide yellow C177492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies ([Table 2](#)) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in [Table 3](#).

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in [Table 4](#).

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see [Table 5](#)).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see [Table 5](#)).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The

^ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in [Table 6](#). Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per [Table 7](#) below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see [Table 8](#)). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

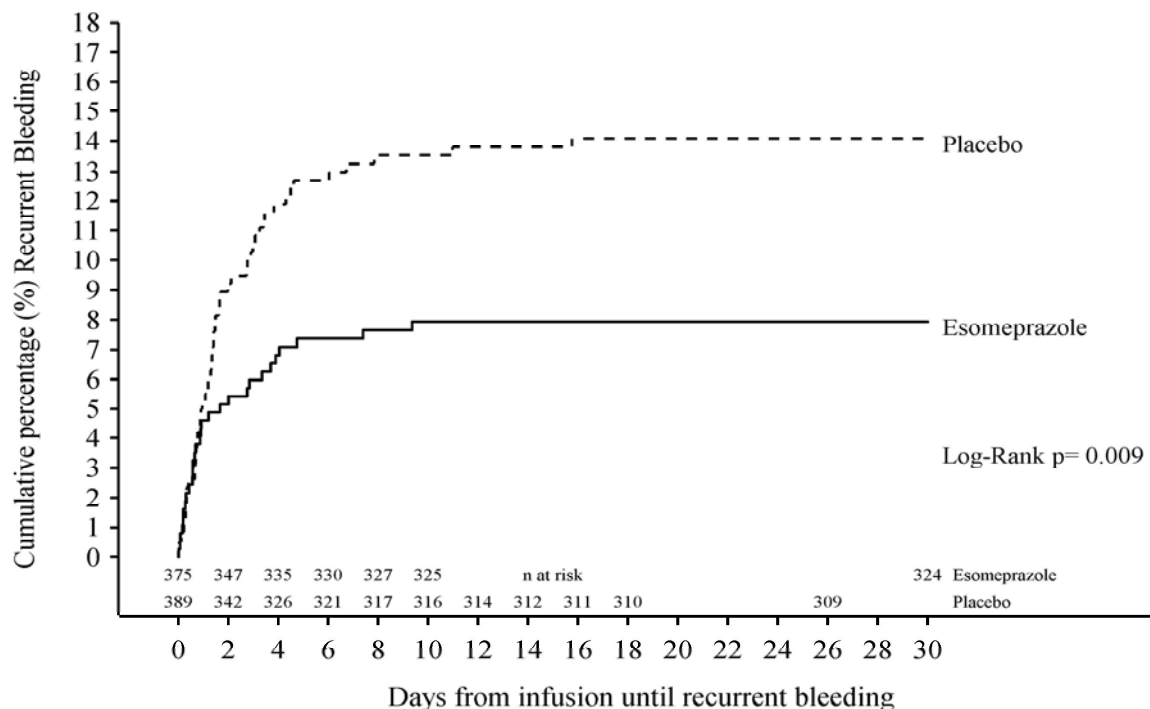
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day

treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD ([Table 9](#))

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH} > 4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were

gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 22 December 2010

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NEXIUM®

esomeprazole magnesium trihydrate

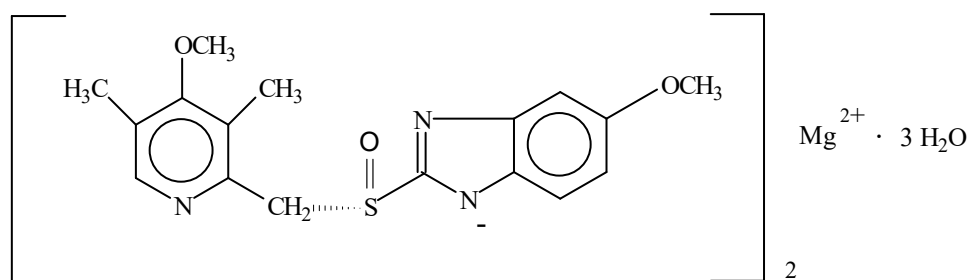
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red C177491. In the 20 mg tablet iron oxide yellow C177492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as

^ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

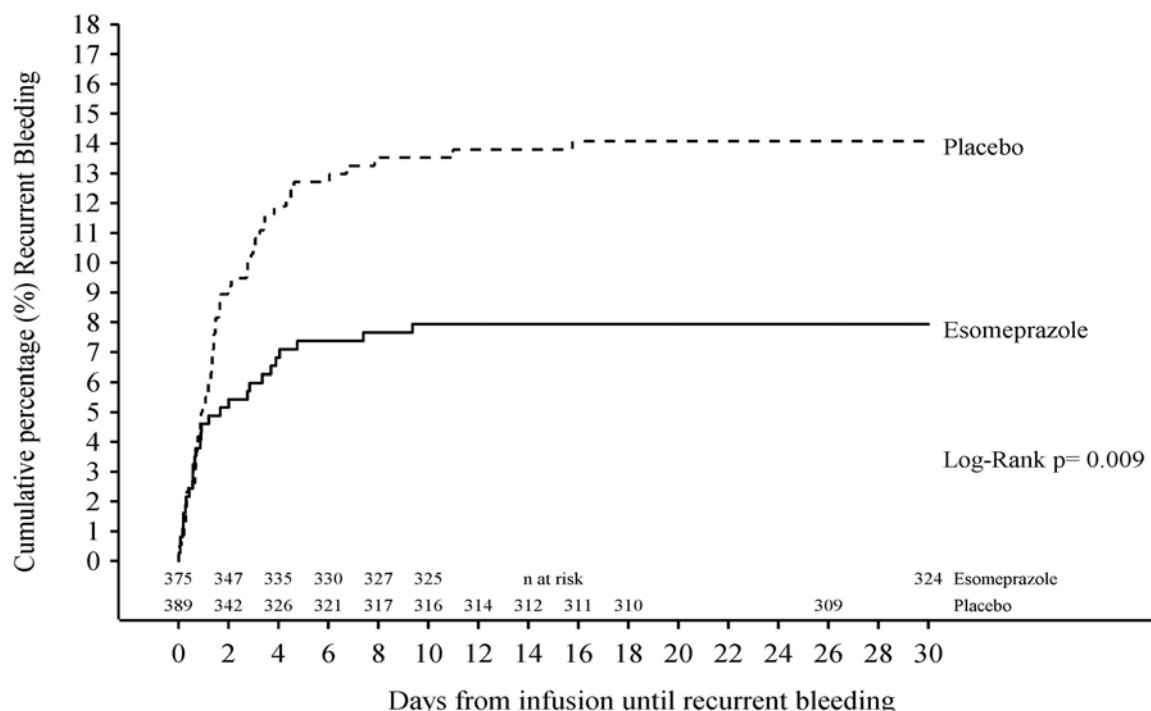
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin

250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C _{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_τ, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For

a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 22 December 2010

Date of most recent amendment: 20 May 2011

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NEXIUM®

esomeprazole magnesium trihydrate

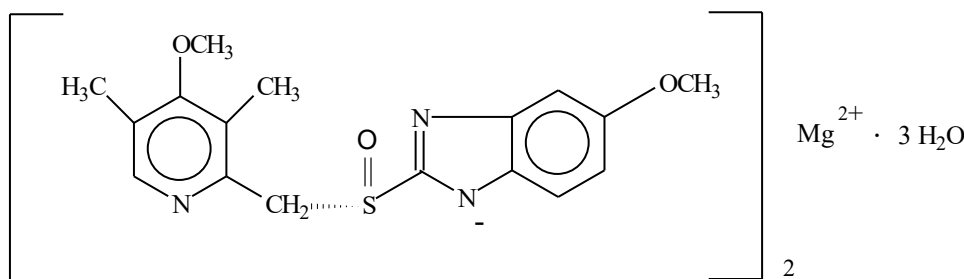
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 20 mg and 40 mg tablet are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Nexium 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as

^ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in Paediatric and Adolescent Patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of Nexium once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper

GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for Nexium 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The Nexium 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on Nexium 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric Ulcer Healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer Prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

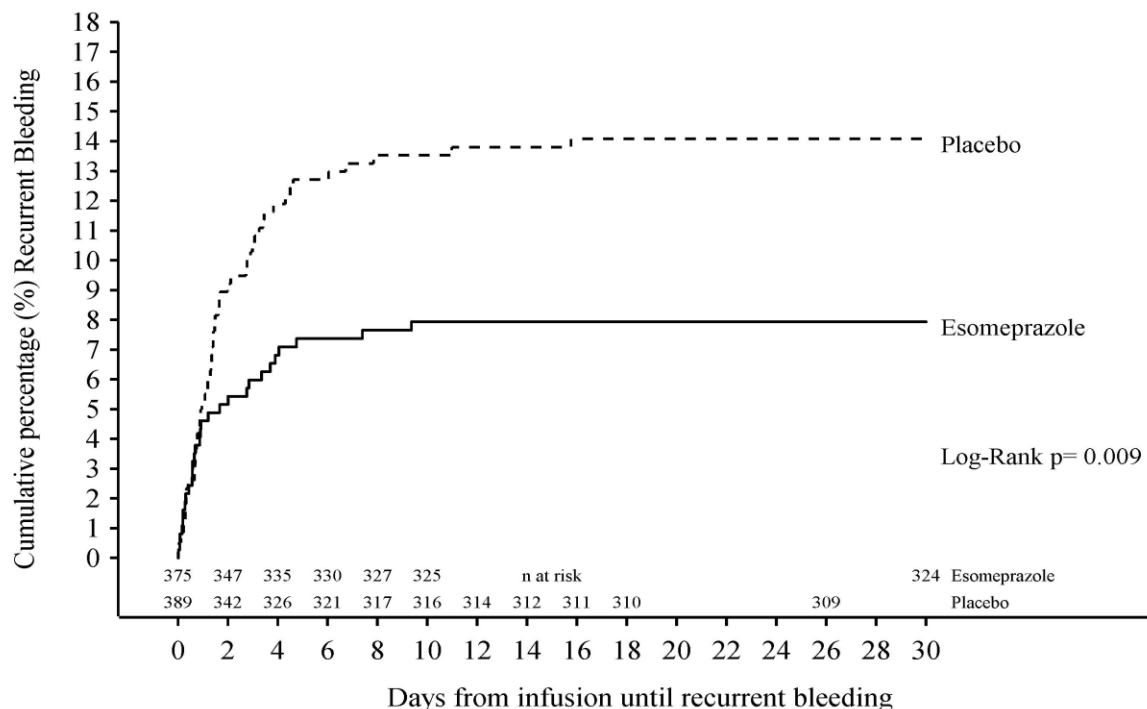
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of Gastric Acid Secretion in Patients with Hypersecretory States

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day

treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was $3.51 \mu\text{mol.h/L}$ for the 1.0 mg/kg dose and $0.65 \mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of $0.85 \mu\text{mol/L}$ and $0.17 \mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH} > 4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

Nexium granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For

a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, Nexium granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and Adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

Nexium 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 40 mg tablet: pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

Nexium 10 mg granules for oral suspension: pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

Nexium tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

Nexium granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
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NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 22 December 2010

Date of most recent amendment: 31 October 2012

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NEXIUM®

esomeprazole magnesium trihydrate

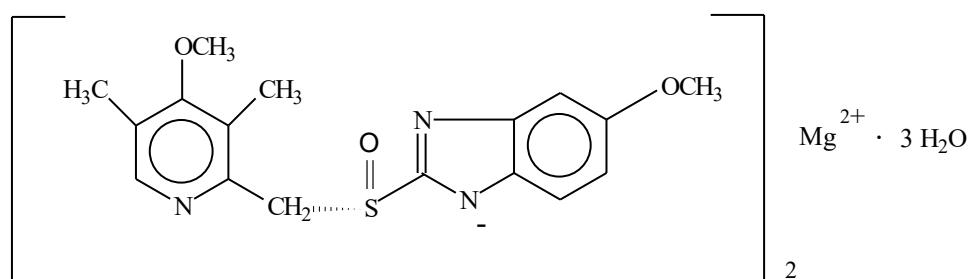
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl

monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see CLINICAL TRIALS).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg

and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009,

E20 $p=0.003$). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 $n=585$; SH-NEN-0014 $n=844$); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

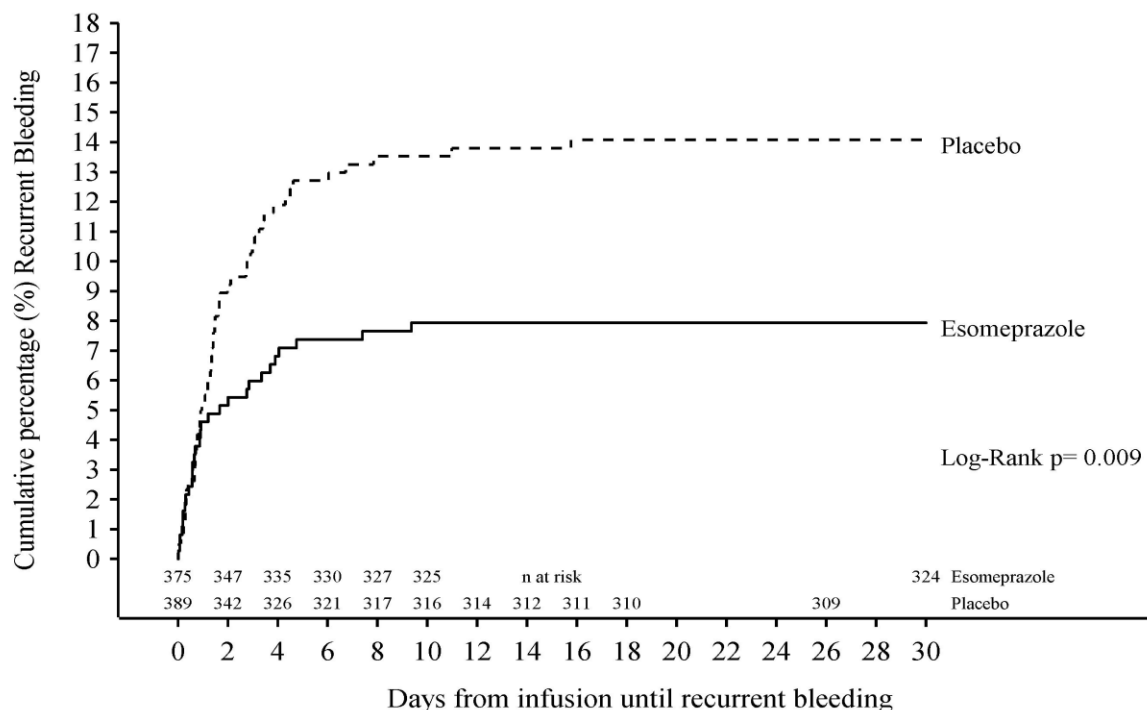
A 26-week randomised double-blind, placebo-controlled trial ($n=992$) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection ($n=375$) or placebo ($n=389$). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6%

respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven

day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Interactions with other medicines).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma

concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C _{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_τ, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

Interactions with other medicines

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For

a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the Clinical Trials section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed. [#]non-marketed pack size

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Date of TGA approval: 22 December 2010

Date of most recent amendment: 9 April 2014

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NEXIUM®

esomeprazole magnesium trihydrate

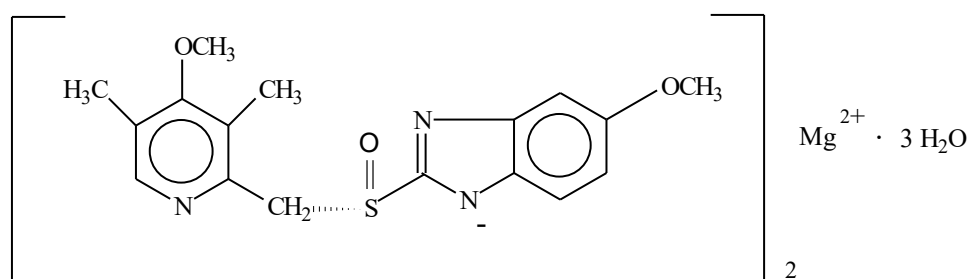
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl

monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum, crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see **CLINICAL TRIALS**).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see **CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis**).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg

and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009,

E20 $p=0.003$). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 $n=585$; SH-NEN-0014 $n=844$); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

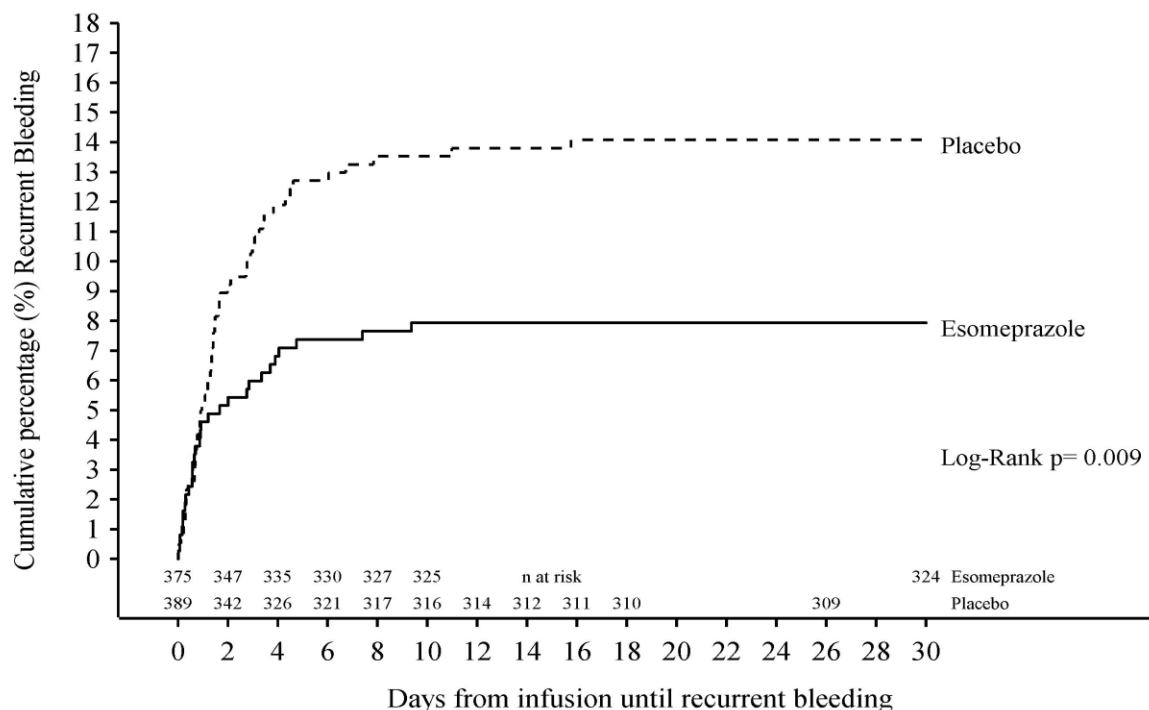
A 26-week randomised double-blind, placebo-controlled trial ($n=992$) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection ($n=375$) or placebo ($n=389$). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6%

respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven

day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer **Effects of esomeprazole on other drugs**)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see **INTERACTIONS WITH OTHER MEDICINES**).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH} > 4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see **DOSAGE AND ADMINISTRATION**).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see **Effects of esomeprazole on other drugs**), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see **PRECAUTIONS**).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated.

Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the **CLINICAL TRIALS** section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see **PRECAUTIONS**).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed. [#]non-marketed pack size

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 December 2010

DATE OF MOST RECENT AMENDMENT

5 June 2014

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NEXIUM®

esomeprazole magnesium trihydrate

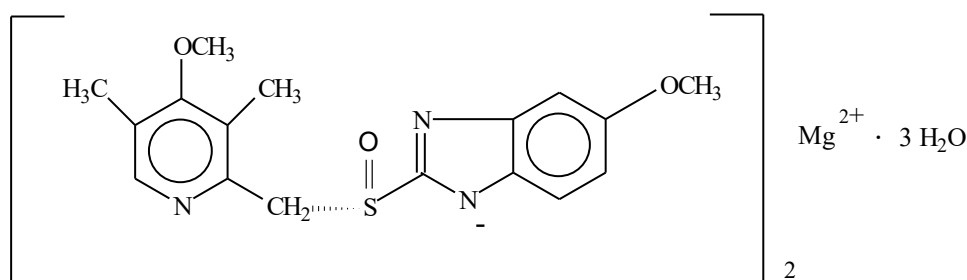
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum,

crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric	% patients with intragastric pH >4 for at least:		
		pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see **CLINICAL TRIALS**).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom

resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific

isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6

month maintenance phase of the study (see **CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis**).

Table 6 The Healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9%

compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or

resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored

without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg

and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

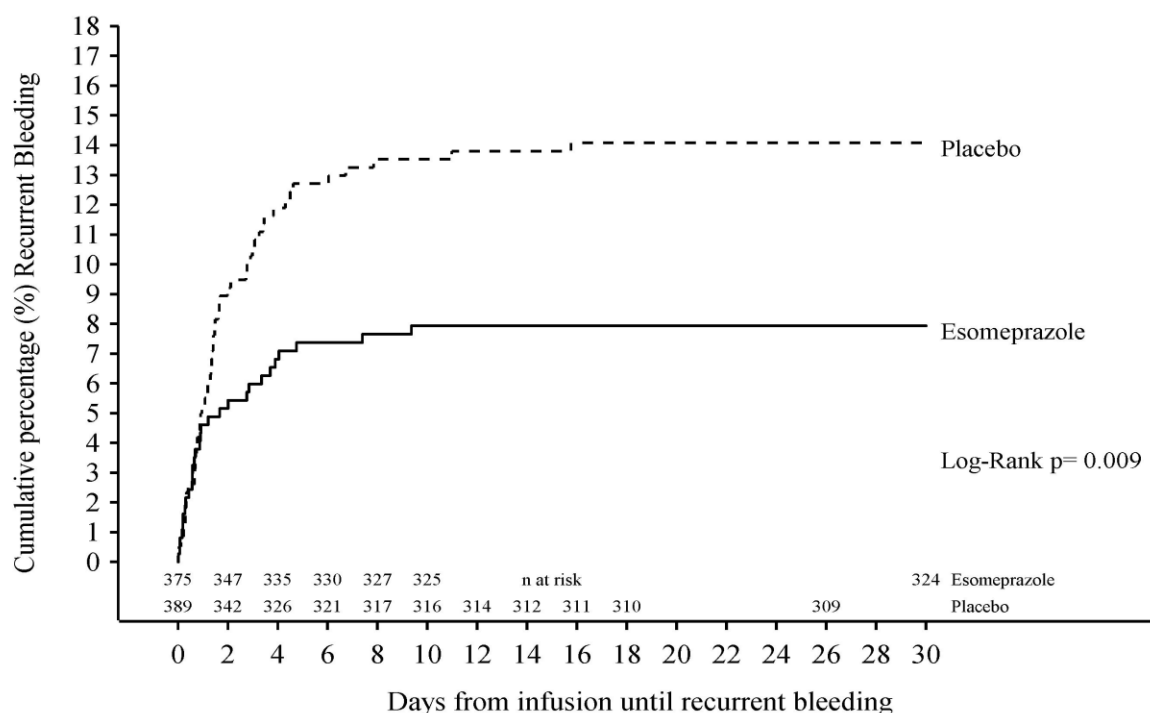
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day

treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer **Effects of esomeprazole on other drugs**)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to

fluctuating plasma concentrations of esomeprazole should be considered (see **INTERACTIONS WITH OTHER MEDICINES**).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered.

Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC (µmol.h/L)	3.65	13.86	4.2	12.6
C _{max} (µmol/L)	1.45	5.13	2.1	4.7
t _{max} (h)	2.00	1.75	1.6	1.6
t _{1/2} (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and t_{1/2}, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC (µmol.h/L)	0.74	4.83	3.70	6.28
C _{max} (µmol/L)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty

patients were randomised of which 43 were ≤ 12 months of age and 7 were > 12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were > 12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_t was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH} > 4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children < 1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see **DOSAGE AND ADMINISTRATION**).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia

and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see **Effects of esomeprazole on other drugs**), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see **PRECAUTIONS**).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg

dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the **CLINICAL TRIALS** section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see **PRECAUTIONS**).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 December 2010

DATE OF MOST RECENT AMENDMENT

6 February 2015

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NEXIUM®

esomeprazole magnesium trihydrate

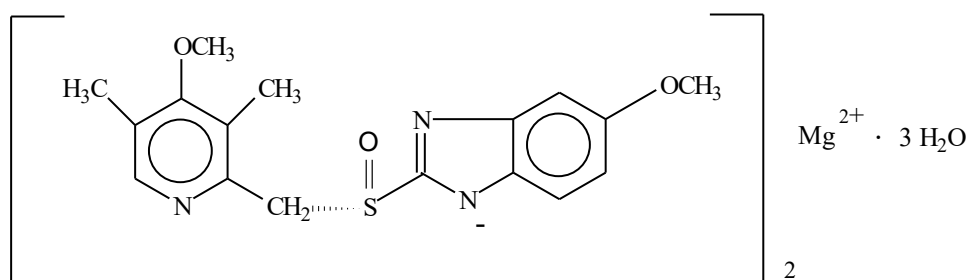
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum,

crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric	% patients with intragastric pH >4 for at least:		
		pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see **CLINICAL TRIALS**).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom

resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific

isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6

month maintenance phase of the study (see **CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis**).

Table 6 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9%

compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or

resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored

without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg

and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

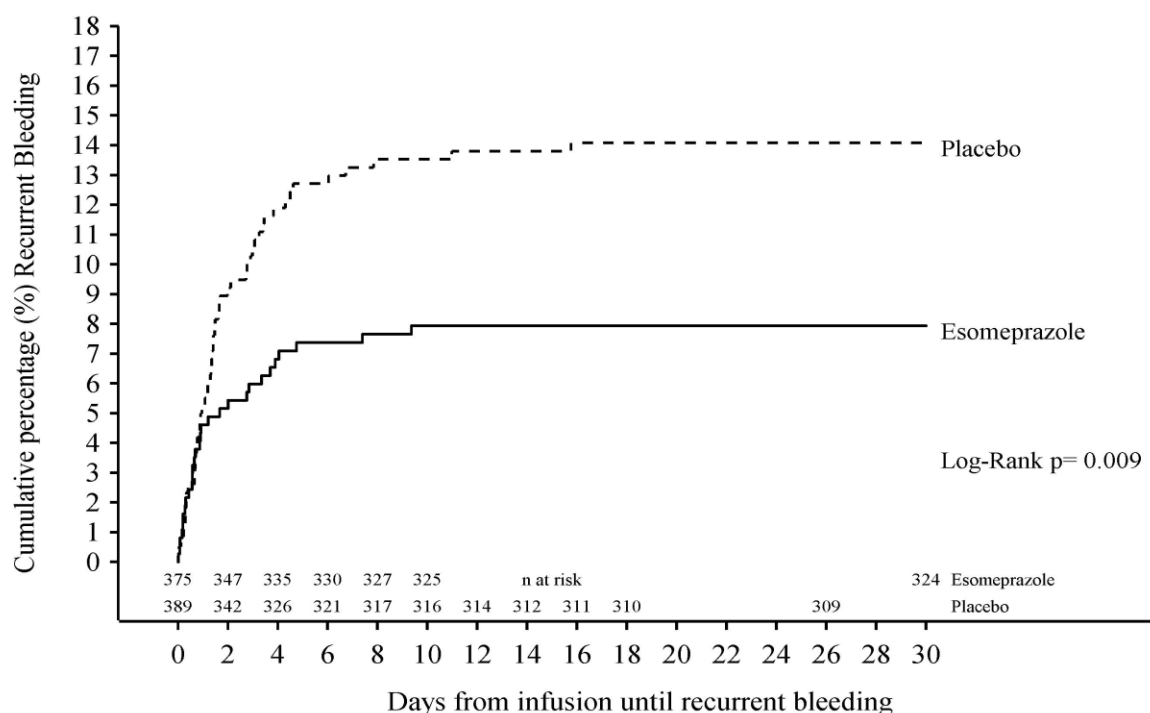
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day

treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer **Effects of esomeprazole on other drugs**)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to

fluctuating plasma concentrations of esomeprazole should be considered (see **INTERACTIONS WITH OTHER MEDICINES**).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered.

Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration ($t_{\max}$) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean $C_{\max}$ values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see **DOSAGE AND ADMINISTRATION**).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see **Effects of esomeprazole on other drugs**), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the

esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see **PRECAUTIONS**).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and

transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the **CLINICAL TRIALS** section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see **PRECAUTIONS**).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 December 2010

DATE OF MOST RECENT AMENDMENT

1 June 2015

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NEXIUM®

esomeprazole magnesium trihydrate

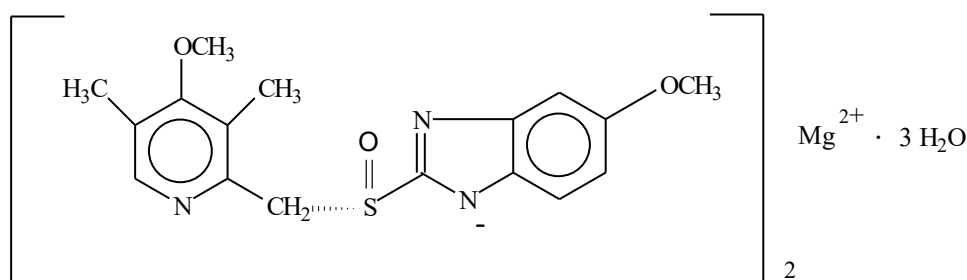
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum,

crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric	% patients with intragastric pH >4 for at least:		
		pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see **CLINICAL TRIALS**).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom

resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific

isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6

month maintenance phase of the study (see **CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis**).

Table 6 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9%

compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or

resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored

without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg

and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

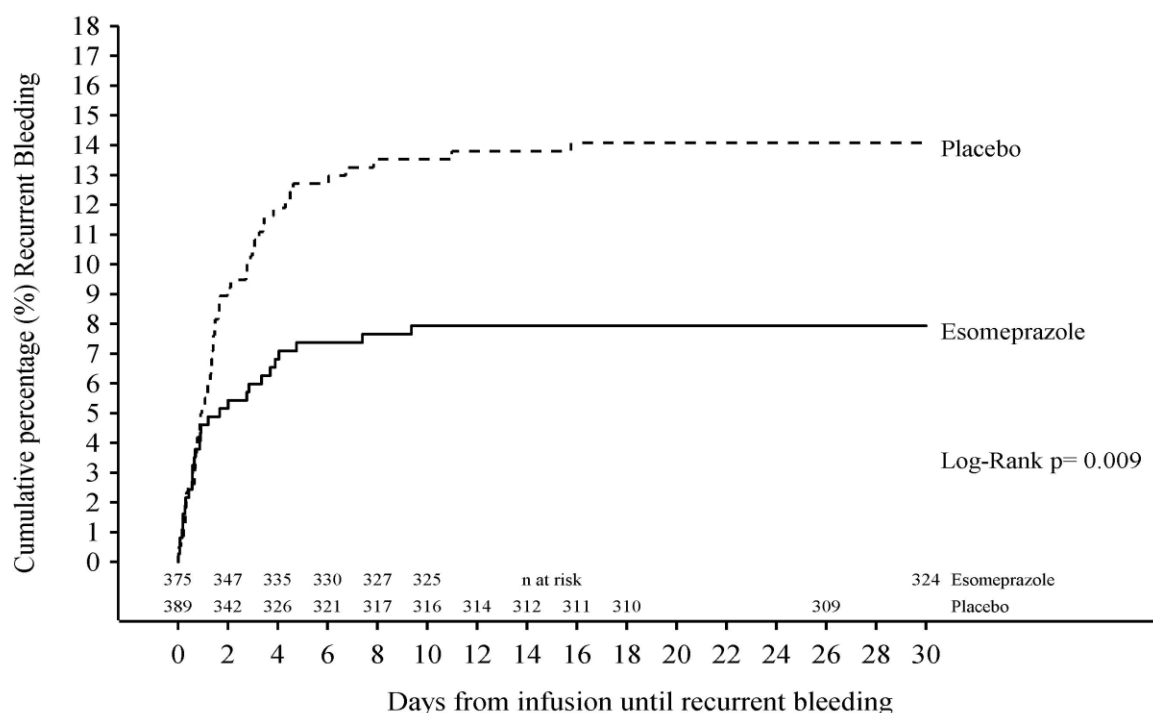
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day

treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer **Effects of esomeprazole on other drugs**)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to

fluctuating plasma concentrations of esomeprazole should be considered (see **INTERACTIONS WITH OTHER MEDICINES**).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered.

Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for

the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC (µmol.h/L)	0.74	4.83	3.70	6.28
C _{max} (µmol/L)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 µmol.h/L for the 1.0 mg/kg dose and 0.65 µmol.h/L for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 µmol/L and 0.17 µmol/L were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_τ, AUC_t, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH>4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see **DOSAGE AND ADMINISTRATION**).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see **Effects of esomeprazole on other drugs**), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see **PRECAUTIONS**).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and

pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the **CLINICAL TRIALS** section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see **PRECAUTIONS**).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

22 December 2010

DATE OF MOST RECENT AMENDMENT

6 July 2015

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NEXIUM®

esomeprazole magnesium trihydrate

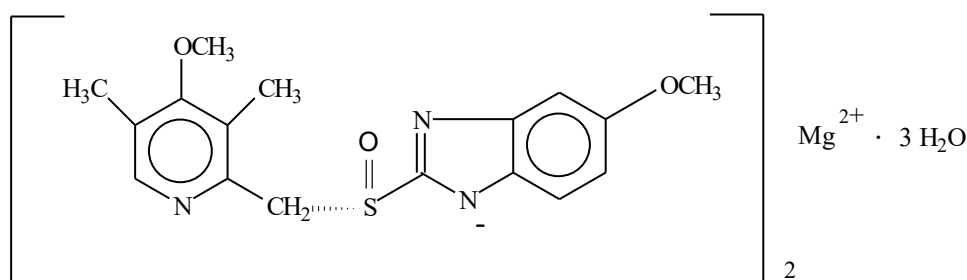
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM is a proton pump inhibitor. The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose – anhydrous, xanthan gum,

crospovidone, citric acid – anhydrous, iron oxide yellow and sugar spheres (maize starch and sucrose).

PHARMACOLOGY

NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 2) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 2 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric	% patients with intragastric pH >4 for at least:		
		pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 3.

Table 3

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 4.

Table 4 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see **CLINICAL TRIALS**).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom

resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific

isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 5).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 5).

Table 5 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 6. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6

month maintenance phase of the study (see **CLINICAL TRIALS - Maintenance treatment of erosive reflux oesophagitis**).

Table 6 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9%

compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 7 below.

Table 7 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or

resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored

without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 8). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 8 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg

and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

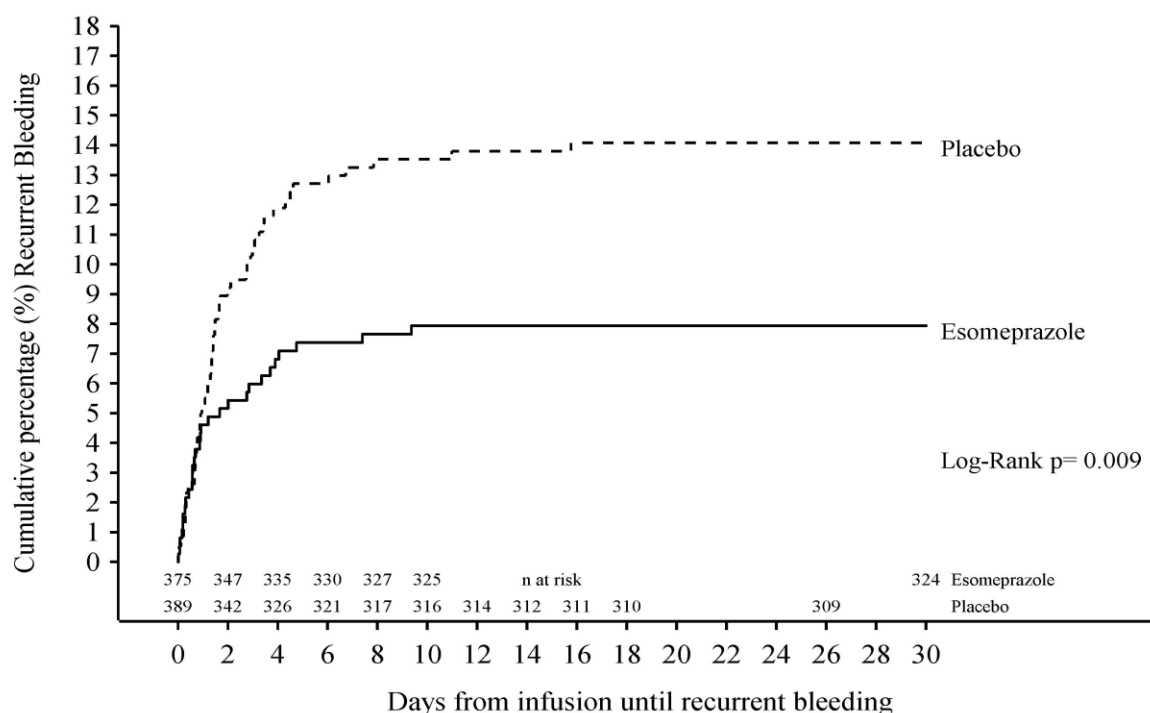
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day

treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer **Effects of esomeprazole on other drugs**)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to

fluctuating plasma concentrations of esomeprazole should be considered (see **INTERACTIONS WITH OTHER MEDICINES**).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered.

Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 9)

Table 9 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for

the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 10 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC (µmol.h/L)	0.74	4.83	3.70	6.28
C _{max} (µmol/L)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 µmol.h/L for the 1.0 mg/kg dose and 0.65 µmol.h/L for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 µmol/L and 0.17 µmol/L were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_τ, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH>4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see **DOSAGE AND ADMINISTRATION**).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast feeding.

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see **Effects of esomeprazole on other drugs**), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see **PRECAUTIONS**).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and

pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 11 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total n=519	E 40 n=173	E 20 n=179	E 10 n=167	Placebo n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In the **CLINICAL TRIALS** section, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see **PRECAUTIONS**).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM tablets and granules for oral suspension: stored below 25°C.

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.
[#]non-marketed pack size

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

22 December 2010

DATE OF MOST RECENT AMENDMENT

27 April 2016

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AUSTRALIAN PRODUCT INFORMATION

NEXIUM®

(esomeprazole magnesium trihydrate)

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole.

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate).

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains excipient of known effect: glucose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the

contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Elderly

Dose adjustment is not required in the elderly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3 CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered.

Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXIUM. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

Use in hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Use in the Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Paediatric use

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC

values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 1).

Table 1 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 2 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration ($t_{\max}$) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean $C_{\max}$ values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH}>4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs section), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is

recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore, NEXIUM should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 3 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 4 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 5) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 5 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric	% patients with intragastric pH >4 for at least:		
		pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 6.

Table 6

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 7.

Table 7 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see Clinical trial section).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical trials section and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 8).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 8).

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Table 8 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 9. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see Maintenance treatment of erosive reflux oesophagitis).

Table 9 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
	Grade B	80.2%	75.4%	0.0002
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 10 below.

Table 10 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of

NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid

regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 11). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 11 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

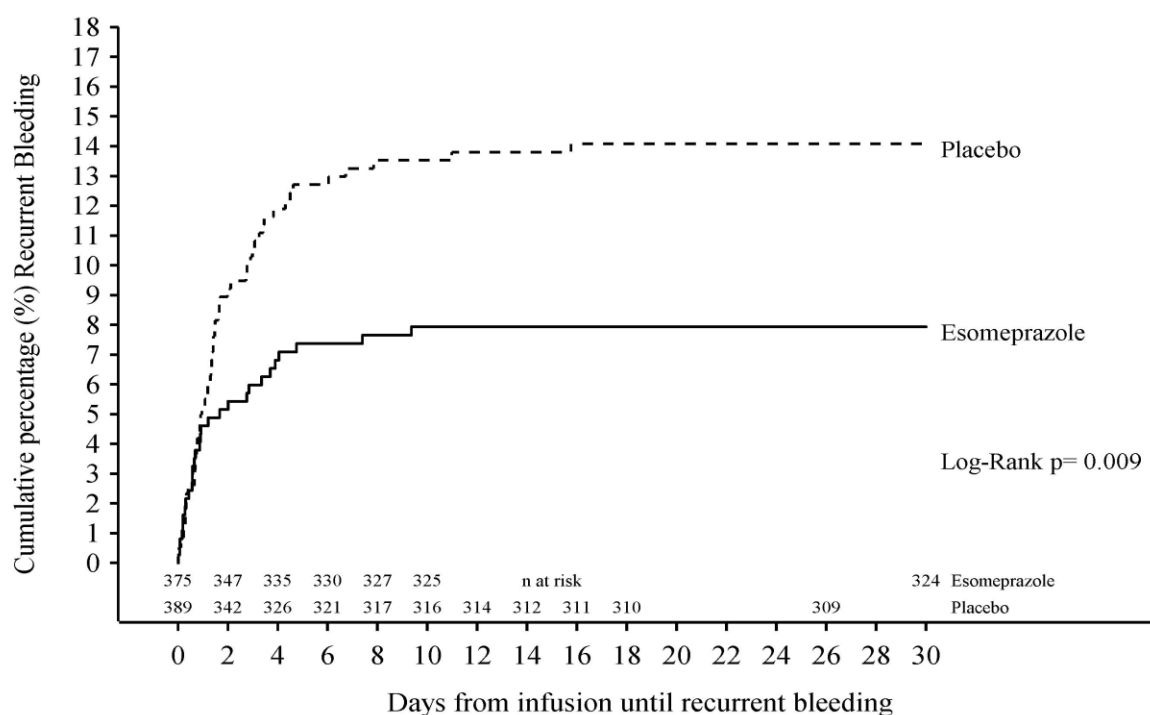
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, p=0.0007, life-table analysis). Esomeprazole 20 mg daily was

also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled

gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

***Helicobacter pylori* eradication**

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia

and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, croscopovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose, xanthan gum, croscopovidone, citric acid, iron oxide yellow and sugar spheres (maize starch and sucrose).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

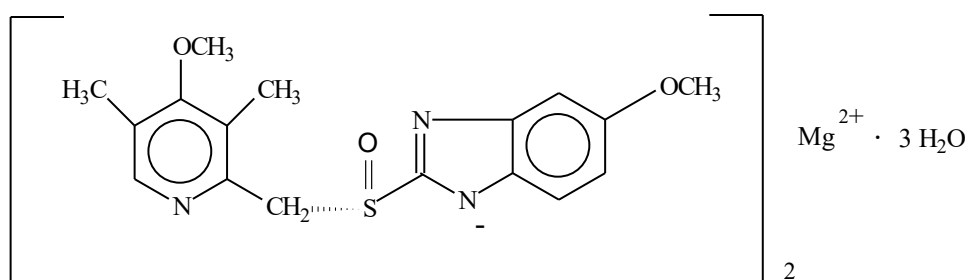
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number

217087-09-7

Molecular formula

$\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight

767.2 (trihydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
Macquarie Park NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

2 April 2019

Summary table of changes

Section changed	Summary of new information
All sections	PI reformatted
4.4	New precaution – subacute cutaneous lupus erythematosus
8	Sponsor details updated

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AUSTRALIAN PRODUCT INFORMATION

NEXIUM®

(esomeprazole magnesium trihydrate)

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole.

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate).

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains excipient of known effect: glucose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the

contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Elderly

Dose adjustment is not required in the elderly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3 CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXIUM. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

Use in hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Use in the Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Paediatric use

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC

values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 1).

Table 1 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 2 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration ($t_{\max}$) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean $C_{\max}$ values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH}>4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs section), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is

recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore, NEXIUM should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Not known: withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 3 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 4 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 5) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 5 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time	% patients with intragastric pH >4 for at least:		
		Intragastric pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 6.

Table 6

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 7.

Table 7 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see Clinical trial section).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical trials section and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 8).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 8).

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Table 8 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 9. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see Maintenance treatment of erosive reflux oesophagitis).

Table 9 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
	Grade B	80.2%	75.4%	0.0002
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 10 below.

Table 10 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of

NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid

regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 11). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 11 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

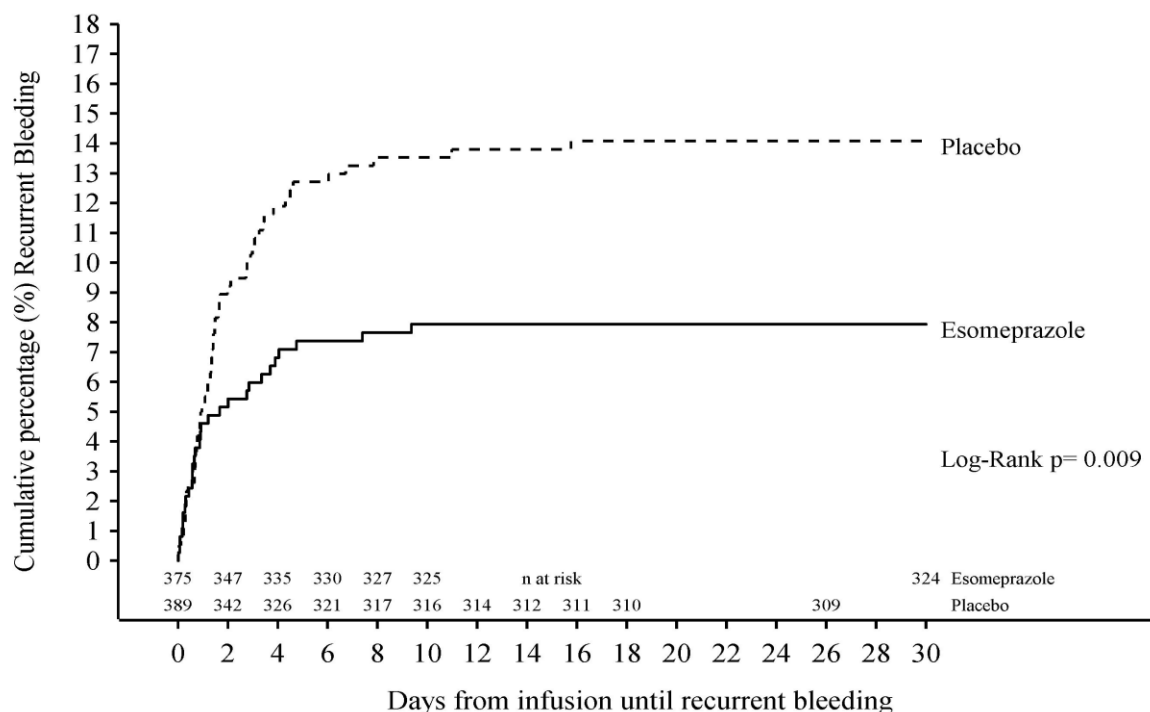
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, p=0.0007, life-table analysis). Esomeprazole 20 mg daily was

also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled

gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

***Helicobacter pylori* eradication**

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia

and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, croscopovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose, xanthan gum, croscopovidone, citric acid, iron oxide yellow and sugar spheres (maize starch and sucrose).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

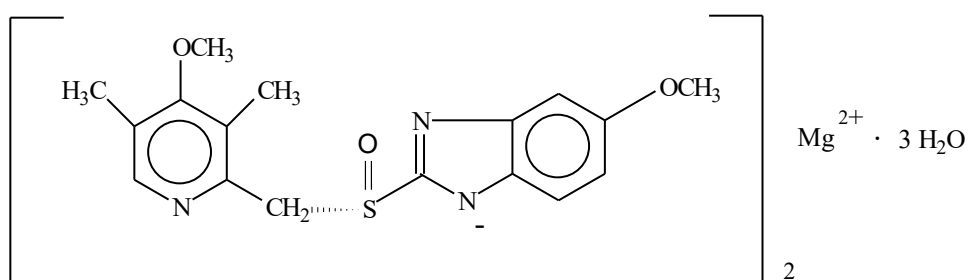
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number

217087-09-7

Molecular formula

$\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight

767.2 (trihydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
Macquarie Park NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

3 July 2019

Summary table of changes

Section changed	Summary of new information
4.8	New adverse effect – rebound acid hypersecretion upon discontinuation of long-term PPI therapy

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AUSTRALIAN PRODUCT INFORMATION

NEXIUM®

(esomeprazole magnesium trihydrate)

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole.

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the

contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Elderly

Dose adjustment is not required in the elderly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3 CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXIUM. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

Use in hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Use in the Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Paediatric use

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC

values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 1).

Table 1 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 2 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C_{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration ($t_{\max}$) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_{τ} was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean $C_{\max}$ values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_{τ} , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric $\text{pH}>4$ increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs section), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is

recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore, NEXIUM should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Not known: withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)

Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 3 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 4 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 5) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 5 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 6.

Table 6

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 7.

Table 7 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see Clinical trial section).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical trials section and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 8).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 8).

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Table 8 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 9. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see Maintenance treatment of erosive reflux oesophagitis).

Table 9 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
	Grade B	80.2%	75.4%	0.0002
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 10 below.

Table 10 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of

NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid

regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 11). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 11 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

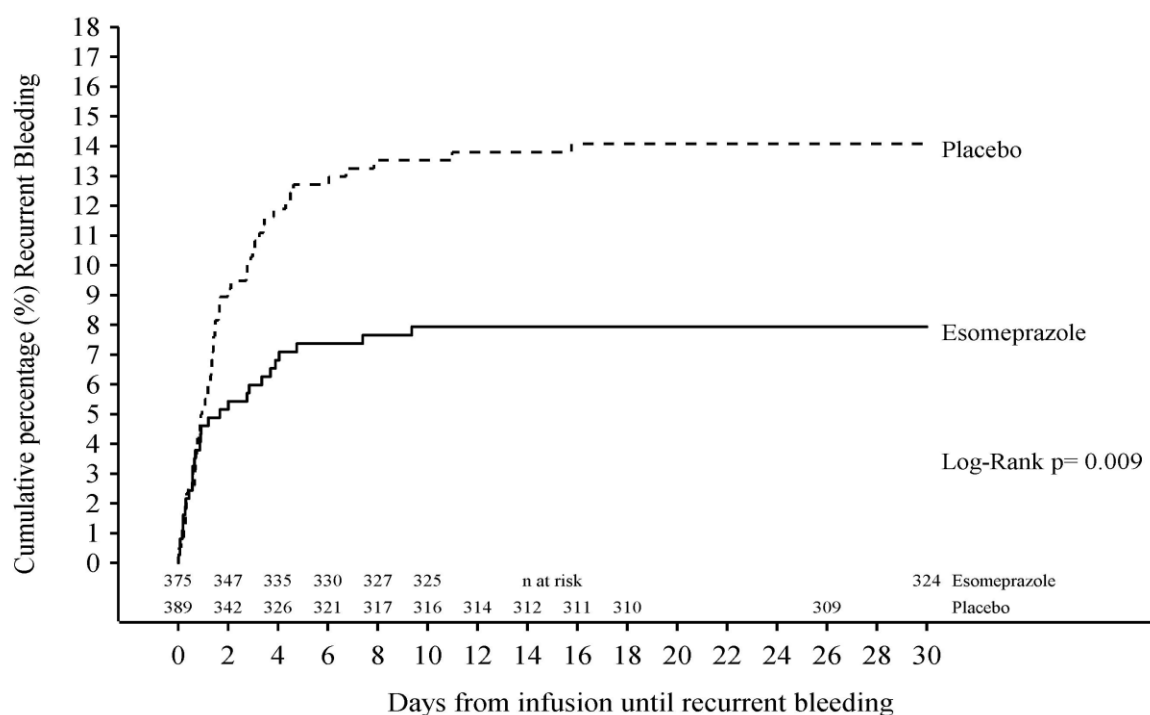
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, p=0.0007, life-table analysis). Esomeprazole 20 mg daily was

also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled

gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

***Helicobacter pylori* eradication**

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia

and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose, xanthan gum, crospovidone, citric acid, iron oxide yellow and sugar spheres (maize starch and sucrose).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

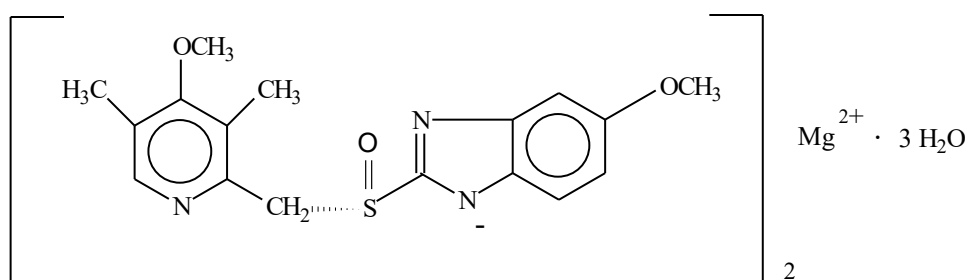
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-(S)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number

217087-09-7

Molecular formula

$\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight

767.2 (trihydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
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Macquarie Park NSW 2113

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9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

23 April 2021

Summary table of changes

Section changed	Summary of new information
2.0	Addition of "Contains sugars"
4.8	New adverse effects – acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS).
Various	Minor editorial changes

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AUSTRALIAN PRODUCT INFORMATION

NEXIUM®

(esomeprazole magnesium trihydrate)

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole.

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the

contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

Weight <20 kg: 10 mg once daily for 8 weeks.
Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Elderly

Dose adjustment is not required in the elderly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3 CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXIUM. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Special patient populations

Use in hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Use in the Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Paediatric use

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 1).

Table 1 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
C_{max} ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, C_{max} and $t_{1/2}$, and median value for t_{max}

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 2 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
C _{max} ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
t _{max} (h)	1.33	1.44	1.79	1.75
t _{1/2} (h)	0.42	0.74	0.88	0.73
CI/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except t_{max} which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_τ was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean C_{max} values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t, AUC_τ, and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is

most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs section), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore, NEXIUM should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia

Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema

Rare: hyponatraemia

Very rare: hypomagnesaemia; hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia

Psychiatric disorders

Uncommon: insomnia

Rare: agitation, confusion, depression

Very rare: aggression, hallucination

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation

Uncommon: dry mouth

Rare: stomatitis, gastrointestinal candidiasis

Very rare: microscopic colitis

Not known: withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal

necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 3 Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 4 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 5) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 5 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time Intragastric pH > 4	% patients with intragastric pH >4 for at least:		
			8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 6.

Table 6

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 7.

Table 7 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	

	n	% time intragastric pH > 4	p-value
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see Clinical trial section).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical trials section and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis

(grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 8).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 8).

Table 8 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg

^ψ The LA Endoscopic Classification system for reflux oesophagitis

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 9. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see Maintenance treatment of erosive reflux oesophagitis).

Table 9 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	0.0002
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	
	Grade D	61.4%	40.2%	
	All	78.8%	72.8%	
Week 8	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with

healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 10 below.

Table 10 Proportion and number of patients who were in remission at 6 months.

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically

significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit (Week 2, Week 4, Week 6, and final visit) for all treatment groups (p <0.0036). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; n=402 and NEN-0003; n=376) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: "How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?" The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 11). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 11 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non-selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not >25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

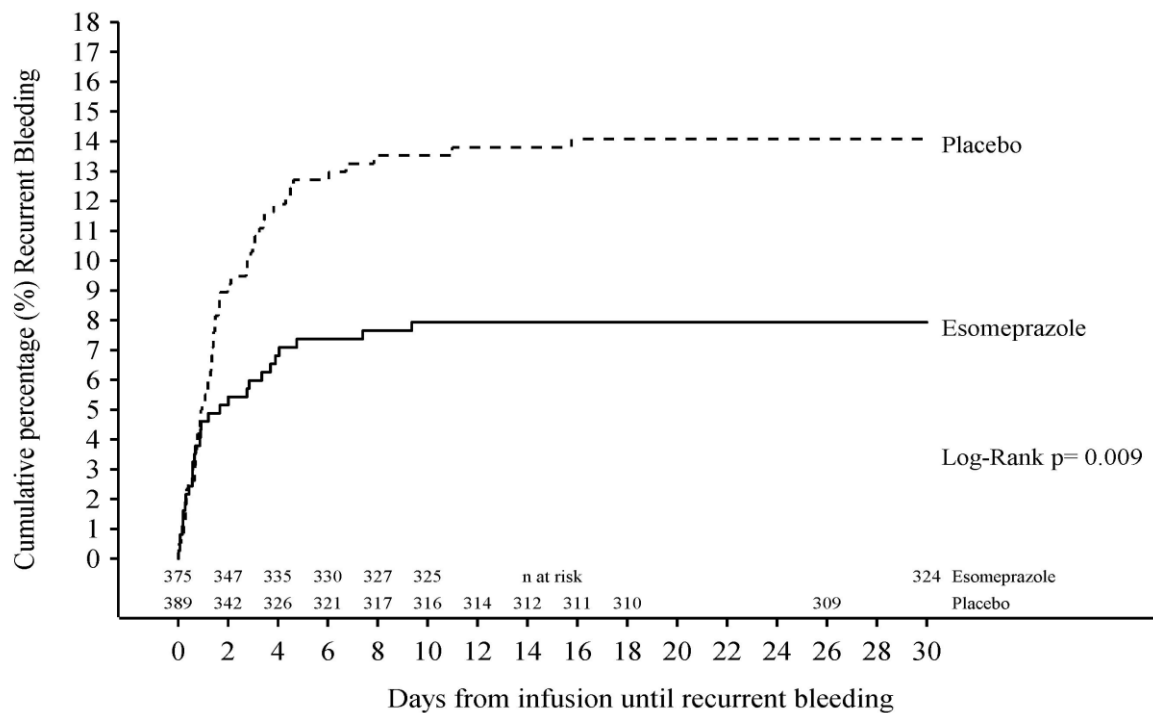
The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, $p=0.0007$, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs 13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate

of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-

dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize

starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid copolymer, polysorbate 80, talc, triethyl citrate, glucose, xanthan gum, crospovidone, citric acid, iron oxide yellow and sugar spheres (maize starch and sucrose).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets and HDPE bottles of 100[#] tablets. Keep bottle tightly closed.

[#]non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

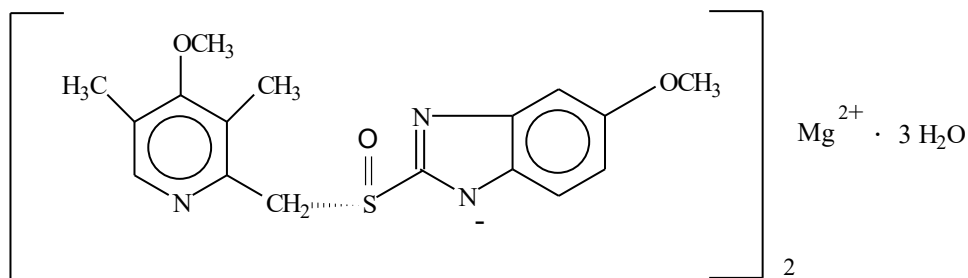
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-(S)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number

217087-09-7

Molecular formula

$\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg} \cdot 3\text{H}_2\text{O}$

Molecular weight

767.2 (trihydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
Macquarie Park NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

16 December 2022

Summary table of changes

Section changed	Summary of new information
4.4	New precaution – hypomagnesaemia.
4.8	Updated adverse effect – hypomagnesaemia.

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AUSTRALIAN PRODUCT INFORMATION
NEXIUM[®]
(esomeprazole magnesium trihydrate)
Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in NEXIUM is esomeprazole magnesium trihydrate, a substituted benzimidazole.

The NEXIUM 20 mg and 40 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

NEXIUM 10 mg granules for oral suspension are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). Contains sugars.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 20 mg tablets are a light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

NEXIUM 40 mg tablets are a pink, oblong, biconvex, film-coated tablet engraved 40 mg on one side and A/EI on the other side. Each tablet contains esomeprazole magnesium trihydrate 44.5 mg as enteric-coated pellets.

NEXIUM 10 mg granules for oral suspension are pale yellow fine granules (brownish granules may be visible) in a unit dose sachet. Each sachet contains esomeprazole magnesium trihydrate 11.1 mg as enteric-coated pellets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEXIUM is indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis

- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

Patients requiring NSAID therapy

- short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.
- healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy
- prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

Prevention of rebleeding of gastric or duodenal ulcers following treatment with NEXIUM IV solution by intravenous infusion.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with *Helicobacter pylori*
- eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer

4.2 DOSE AND METHOD OF ADMINISTRATION

Tablets

NEXIUM tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered via a large syringe through a gastric tube. To ensure appropriate dosing and to avoid clogging, the gastric tube should be flushed with non-carbonated water following administration.

Oral suspension

NEXIUM granules for oral suspension should be dispersed in an appropriate amount of non-carbonated water (mineral water is not suitable). For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 mL of water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 mL of water. Stir the contents and leave for a

few minutes to thicken. Stir again and drink within 30 minutes. If any material remains after drinking, add more water, stir and drink immediately.

For patients who cannot swallow, NEXIUM granules for oral suspension can be administered via a large syringe through a nasogastric or gastric tube. For a 10 mg dose add the contents of a 10 mg sachet to a syringe containing 15 mL of water. For a 20 mg dose add the contents of two 10 mg sachets to a syringe containing 30 mL of water. Immediately shake the syringe and leave for a few minutes to thicken. Shake the syringe and inject through the nasogastric or gastric tube within 30 minutes. Refill the syringe with 15 mL of water and shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

Adults

Gastro-Oesophageal Reflux Disease (GORD)

Treatment of erosive reflux oesophagitis

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily.

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. For patients with symptom resolution after 4 weeks initial therapy, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

Patients requiring NSAID (non-selective and COX-2 selective) therapy

Short-term treatment of upper gastrointestinal symptoms associated with NSAID therapy

20 mg once daily in patients requiring NSAID therapy. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Controlled studies did not extend beyond 4 weeks.

Healing of gastric ulcers associated with NSAID (non-selective and COX-2 selective) therapy

The usual dose is 20 mg once daily for 4 to 8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID (non-selective and COX-2 selective) therapy in patients at risk

20 mg once daily. Controlled studies did not extend beyond 6 months.

Prevention of rebleeding of gastric or duodenal ulcers

40 mg once daily for a duration determined by the treating physician. Oral NEXIUM should be preceded by esomeprazole administered intravenously.

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion

The recommended initial dosage is NEXIUM 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been administered.

In combination with appropriate antibiotics for:

- Healing of duodenal ulcer associated with *Helicobacter pylori*
- Eradication of *Helicobacter pylori* with active or healed peptic ulceration

20 mg NEXIUM twice daily for 7 days. In Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials, NEXIUM was used in combination with 1000 mg amoxicillin and 500 mg clarithromycin, both twice daily for 7 days.

Children and adolescents 12-18 years***Treatment of erosive reflux oesophagitis***

40 mg once daily for four weeks.

An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

20 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In patients with normal endoscopy 20 mg once daily for four weeks. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily under medical supervision.

Children 1-11 years***Gastro-Oesophageal Reflux Disease (GORD)******Treatment of erosive reflux oesophagitis***

Weight <20 kg:	10 mg once daily for 8 weeks.
Weight ≥20 kg:	10 mg or 20 mg once daily for 8 weeks.

Long-term management (maintenance) of patients with healed oesophagitis to prevent relapse

10 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (GORD)

10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg have not been studied.

Children below the age of 1 year

NEXIUM is not approved for use in children younger than 1 year.

Elderly

Dose adjustment is not required in the elderly.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3 CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute tubulointerstitial nephritis

Acute tubulointerstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including esomeprazole. Acute tubulointerstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Acute tubulointerstitial nephritis can progress to renal failure. Discontinue esomeprazole if acute tubulointerstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXIUM. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Special patient populations

Use in hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Use in the Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Paediatric use

Children 12-18 years

The pharmacokinetics of esomeprazole were studied in 28 adolescent patients with GORD aged 12 to 18 years, in a single centre study. Patients were randomised to receive esomeprazole 20 mg or 40 mg once daily for 8 days. Mean $C_{\max}$ and AUC values of esomeprazole were not affected by body weight or age; and more than dose proportional increases in mean $C_{\max}$ and AUC values were observed between the two dose groups in the study. Overall, esomeprazole pharmacokinetics in adolescent patients aged 12 to 18 years were similar to those observed in adult patients with symptomatic GORD (Table 1).

Table 1 Comparison of PK Parameters in 12 to 18 Year Olds with GORD and Adults with Symptomatic GORD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

	12-18 Year Olds (n=28)		Adults (n=36)	
	20 mg	40 mg	20 mg	40 mg
AUC ($\mu\text{mol.h/L}$)	3.65	13.86	4.2	12.6
$C_{\max}$ ($\mu\text{mol/L}$)	1.45	5.13	2.1	4.7
$t_{\max}$ (h)	2.00	1.75	1.6	1.6
$t_{1/2}$ (h)	0.82	1.22	1.2	1.5

*Duration of treatment for 12 to 18 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Data presented are geometric means for AUC, $C_{\max}$ and $t_{1/2}$, and median value for $t_{\max}$

Children 1-11 years

Following repeated dose administration of 10 mg and 20 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration ($t_{\max}$) for the 10 mg dose was similar across the 1 to 11 year-olds and similar to the total exposure seen with the 20 mg dose in 12 to 18 year-olds and adults. The 20 mg dose resulted in higher exposure in 6 to 11 year-olds compared to 12 to 18 year-olds and adults.

Table 2 Summary of Pharmacokinetic Parameters in 1-11 year olds with GORD following 5 days of once-daily oral esomeprazole treatment

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)
AUC ($\mu\text{mol.h/L}$)	0.74	4.83	3.70	6.28
$C_{\max}$ ($\mu\text{mol/L}$)	0.62	2.98	1.77	3.73
$t_{\max}$ (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except $t_{\max}$ which is the arithmetic mean

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 to 5 year-olds.

A single-centre, randomised, single-blind, two-arm parallel, repeated dose study examined the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants aged 1-24 months. Patients were randomised to either esomeprazole 0.25 mg/kg or 1.0 mg/kg orally once daily for 7 or 8 days. Fifty patients were randomised of which 43 were ≤ 12 months of age and 7 were >12 months of age. Forty-five patients completed the study of whom 39 were ≤ 12 months of age and 6 were >12 months of age. The median time to reach maximum plasma concentration ($t_{\max}$) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. Mean AUC_t was 3.51 $\mu\text{mol.h/L}$ for the 1.0 mg/kg dose and 0.65 $\mu\text{mol.h/L}$ for the 0.25 mg/kg dose. Mean $C_{\max}$ values of 0.85 $\mu\text{mol/L}$ and 0.17 $\mu\text{mol/L}$ were obtained for the 1.0 mg/kg and 0.25 mg/kg doses respectively. Large inter-individual variability in AUC_t , AUC_t , and C_{SSmax} of esomeprazole was observed for both 0.25 mg/kg and 1.0 mg/kg doses and the variability seemed larger in the younger children. No conclusions regarding dose proportionality could be drawn. The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group. Statistically, the increase was significantly higher with esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose. Both doses of esomeprazole were well tolerated. NEXIUM is not approved for use in children <1 year of age.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs section), the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The

slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs such as nelfinavir is not recommended.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Esomeprazole is an enantiomer of omeprazole. Co-administration of omeprazole and mycophenolate mofetil in healthy and transplant patients

has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving proton pump inhibitors and mycophenolate mofetil. Use esomeprazole with caution in transplant patients receiving mycophenolate mofetil.

Potential interactions that have been excluded

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore, NEXIUM should not be used during breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis
Not known: withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: increased liver enzymes

Rare: Hepatitis with or without jaundice

Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash

Rare: alopecia, photosensitivity

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)

Not known: subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia

Very rare: muscular weakness

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (with possible progression to renal failure)

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

Table 3 **Number (%) of patients by the most common adverse events and dose, for long-term maintenance studies (B4 and B5)**

	E total	E 40	E 20	E 10	Placebo
	n=519	n=173	n=179	n=167	n=169
Mean exposure time (days):	136	147	144	115	58
Respiratory infection	44 (8.5)	16 (9.2)	17 (9.5)	11 (6.6)	5 (3.0)
Diarrhoea	35 (6.7)	13 (7.5)	9 (5.0)	13 (7.8)	5 (3.0)
Headache	34 (6.6)	11 (6.4)	14 (7.8)	9 (5.4)	7 (4.1)
Gastritis/gastritis (aggravated)	32 (6.2)	11 (6.4)	13 (7.3)	8 (4.8)	9 (5.3)
Flatulence	26 (5.0)	13 (7.5)	7 (3.9)	6 (3.6)	3 (1.8)
Nausea/nausea (aggravated)	25 (4.8)	11 (6.4)	8 (4.5)	6 (3.6)	4 (2.4)
Sinusitis	22 (4.2)	8 (4.6)	10 (5.6)	4 (2.4)	3 (1.8)
Abdominal pain	19 (3.7)	4 (2.3)	9 (5.0)	6 (3.6)	4 (2.4)
Accident and/or injury	19 (3.7)	3 (1.7)	6 (3.4)	10 (6.0)	3 (1.8)
Infection viral	19 (3.7)	7 (4.0)	7 (3.9)	5 (3.0)	3 (1.8)
Vomiting/vomiting (aggravated)	17 (3.3)	6 (3.5)	3 (1.7)	8 (4.8)	2 (1.2)
Hypertension/hypertension (aggravated)	14 (2.7)	2 (1.2)	6 (3.4)	6 (3.6)	0
Gastrin serum increased	13 (2.5)	6 (3.5)	6 (3.4)	1 (0.6)	0
Tooth disorder	13 (2.5)	4 (2.3)	6 (3.4)	3 (1.8)	1 (0.6)
Back pain	10 (1.9)	3 (1.7)	2 (1.1)	5 (3.0)	4 (2.4)
Epigastric pain/epigastric pain (aggravated)	9 (1.7)	2 (1.2)	2 (1.1)	5 (3.0)	3 (1.8)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

NEXIUM is a proton pump inhibitor. NEXIUM (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+ , K^+ -ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 4 **% GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours**

Population	Study drug	% GORD patients with intragastric pH >4 for at least:		
		8 hours	12 hours	16 hours
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%
GORD (n=115)	Omeprazole 40 mg	96%	77%	45%
	Esomeprazole 40 mg	99%	88%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

In separate comparative studies (Table 5) the time and % patients with an intragastric pH above 4 after five days of oral dosing was compared for esomeprazole 40 mg, pantoprazole 40 mg, and lansoprazole 30 mg and rabeprazole 20 mg. The results from these pharmacodynamic studies are tabulated below.

Table 5 Time and % patients with intragastric pH >4 for different treatment regimens

Population	Study drug	Time	% patients with intragastric pH >4 for at least:		
		Intragastric pH > 4	8 hours	12 hours	16 hours
Symptomatic GORD (n=31)	Esomeprazole 40 mg	16.1 hours*	100%	90%	50%
	Pantoprazole 40 mg	10.8 hours	80%	30%	10%
Healthy (n=30)	Esomeprazole 40 mg	15.7 hours*	95%	90%	38%
	Lansoprazole 30 mg	12.7 hours	95%	57%	5%
Healthy (n=22)	Esomeprazole 40 mg	14.6 hours	-	77%	32%
	Rabeprazole 20 mg	10.8 hours	-	36%	5%

* p <0.001

In a five-way crossover study, the 24 hour intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg once daily was evaluated in 34 symptomatic GORD patients. The results are tabulated below in Table 6.

Table 6 Mean time intragastric pH >4 and % patients with intragastric pH >4 for at least 12 hours for different treatment regimens in symptomatic GORD patients over 24 hours

Population	Study Drug	Mean Time Intragastric pH >4	% Patients with Intragastric pH >4 for at least 12 hours
Symptomatic GORD (n=34)	Esomeprazole 40 mg	14 hours	65%
	Lansoprazole 30 mg	11.5 hours	41%
	Omeprazole 20 mg	12 hours	44%
	Pantoprazole 40 mg	10 hours	32%
	Rabeprazole 20 mg	12 hours	38%

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80

mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 7.

Table 7 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks (see Clinical trial section).

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients and there appears to be a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with active or healed peptic ulcer (see Clinical trials section and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers. Eradication of *H. pylori* is also associated with long-term remission of peptic ulcer disease, thus reducing complications such as gastrointestinal bleeding, as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Healing of erosive reflux oesophagitis

Randomised double-blind clinical trials (n=15,120) were evaluated to assess the comparative efficacy of esomeprazole in the healing of erosive reflux oesophagitis (grades A to D, according to the Los Angeles endoscopic classification system^ψ) after four and eight weeks treatment. A secondary outcome measure was gastro-oesophageal symptom resolution. These trials compared esomeprazole 40 mg and/or 20 mg with the standard dose of omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg.

Esomeprazole 40 mg vs esomeprazole 20 mg vs omeprazole 20 mg

In study B1, the endoscopic healing rates at 4 and 8 weeks and the proportion of patients reporting resolution of symptoms (complete resolution of heartburn and acid regurgitation) were statistically higher for esomeprazole 40 mg compared to omeprazole 20 mg (see Table 8).

Esomeprazole 20 mg vs omeprazole 20 mg

In study B3, the healing rates were comparable for esomeprazole 20 mg and omeprazole 20 mg (see Table 8).

^ψ **The LA Endoscopic Classification system for reflux oesophagitis**

Grade A. One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B. One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds.

Grade C. One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.

Grade D. One (or more) mucosal break, which involves at least 75% of the oesophageal circumference.

Table 8 Erosive reflux oesophagitis healing rates at week 4 and 8

Study	Esomeprazole 40 mg od	Esomeprazole 20 mg od	Omeprazole 20 mg od
B1	4 wks 71.1% (n=654)	4 wks 66.5% (n=656)	4 wks 61.4% (n=650)
	8 wks 87.6% (n=654)	8 wks 83.8% (n=656)	8 wks 81.4% (n=650)
B3	-	4 wks 66.4% (n=587)	4 wks 65.6% (n=588)
	-	8 wks 86.5% (n=587)	8 wks 82.3% (n=588)

Based on pooled data from all clinical trials in patients with baseline endoscopy grades B to D, healing rates at 4 and 8 weeks were statistically significantly better for esomeprazole 40 mg, compared with omeprazole 20 mg.

Esomeprazole 40 mg vs lansoprazole 30 mg

In a randomised, double blind, parallel group trial (n=5,241), the endoscopic healing rates at 4 and 8 weeks were statistically significantly higher for esomeprazole 40 mg compared to lansoprazole 30 mg. Sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.

Esomeprazole 40 mg vs pantoprazole 40 mg (EXPO Study)

In the healing phase of the EXPO study, a randomised, double-blind, multi-centre study (n=3,170), esomeprazole 40 mg had significantly more patients healed on endoscopic assessment at 4 and 8 weeks compared to pantoprazole 40 mg. The proportions of patients with complete healing of reflux oesophagitis by week 8 as per Kaplan-Meier life table estimates were 95.5% (95% CI, 94.43-96.58%) and 92.0% (95% CI, 90.65-93.41%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.0006) (Primary Efficacy). When adjusted for severity of initial oesophagitis using the LA classification system, the proportions of patients healed at 8 weeks were 91.6% (95% CI, 90.1-92.9%) and 88.9% (95% CI, 87.3-90.4%) respectively for esomeprazole 40mg dose and pantoprazole 40 mg dose (p=0.018) (Secondary Efficacy). The crude healing rates after 4 and 8 weeks are given together with the percentages of healed patients for each baseline LA grade in Table 9. Sustained heartburn resolution was achieved significantly faster in patients treated with esomeprazole. The proportion of heartburn-free days was also significantly greater in esomeprazole patients. Endoscopically healed patients free of moderate/severe heartburn and acid regurgitation at 4 or 8 weeks entered the 6 month maintenance phase of the study (see Maintenance treatment of erosive reflux oesophagitis).

Table 9 The healing of reflux oesophagitis by baseline LA classification grade

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 4	Grade A	83.9%	83.1%	
	Grade B	80.2%	75.4%	
	Grade C	71.1%	60.1%	

Time Point	LA grade at baseline	Esomeprazole 40 mg n=1,562	Pantoprazole 40 mg n=1,589	p-value
Week 8	Grade D	61.4%	40.2%	0.0002
	All	78.8%	72.8%	
	Grade A	93.7%	92.5%	0.018
	Grade B	92.3%	90.4%	
	Grade C	87.8%	84.8%	
	Grade D	85.7%	72.8%	
	All	91.6%	88.9%	

Maintenance treatment of erosive reflux oesophagitis

Two randomised double-blind placebo controlled clinical trials (n=750) were evaluated to assess the comparative efficacy of esomeprazole in patients with healed erosive reflux oesophagitis at 1, 2 and 6 months treatment comparing esomeprazole 40 mg or esomeprazole 20 mg or esomeprazole 10 mg with placebo.

Across both studies, maintenance of healing of erosive reflux oesophagitis at 6 months was achieved in a dose-dependent pattern and these results were significantly different from placebo. There were no differences between the esomeprazole 20 mg and 40 mg group of patients.

In the maintenance phase of the EXPO study, endoscopic and symptomatic remission rates in patients with endoscopically healed erosive oesophagitis (n=2,766) were compared in treatment groups receiving either esomeprazole 20 mg or pantoprazole 20 mg once daily for 6 months. Patients were randomised to receive maintenance treatment independent of the treatment used in the healing phase. A significantly higher proportion of patients were in endoscopic and symptomatic remission during 6 months of treatment with esomeprazole 20 mg daily (87.0% [95% CI, 85.1-88.9%] at six months) compared to pantoprazole 20 mg daily (74.9% [95% CI, 72.5-77.3%] at six months) (p-value <0.0001) as per cumulative life table estimates (Primary Efficacy). The proportion of patients in remission at 6 months, when adjusted for severity of initial oesophagitis using the LA classification system, receiving esomeprazole for the healing and maintenance phase was 70.9% compared to 59.6% of patients receiving pantoprazole for the healing and maintenance phases (p-value <0.0001) as per Table 10 below.

Table 10 **Proportion and number of patients who were in remission at 6 months.**

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade A	76.4%	68.1%	
Grade B	72.8%	58.2%	
Grade C	61.6%	53.7%	

LA grade at baseline	Esomeprazole n=772	Pantoprazole n=797	p-value
Grade D	52.6%	44.0%	
All	70.9%	59.6%	<0.0001

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

Treatment of GORD in paediatric and adolescent patients (1-18 years)

A randomised, double-blind multi-centre study was conducted to determine the safety and efficacy in patients with clinically diagnosed GORD aged 12 to 17 years, inclusive (n=149) treated with esomeprazole 20 mg or 40 mg daily. This study was primarily designed as a safety study with a secondary objective to evaluate the clinical outcome. Both doses of esomeprazole were safe and well tolerated with the adverse event profile of this population being consistent with the adverse event profile seen in adults. No clinically important findings or trends in haematology, clinical chemistry, vital signs or physical examination were observed. GORD symptoms were statistically significantly reduced after treatment with esomeprazole. Symptoms (heartburn, acid regurgitation, epigastric pain, vomiting) were reduced or resolved in both the 20 mg (72.4%) and 40 mg (75.3%) treatment arms over the 8 week study period.

A multi-centre, parallel-group study was conducted in 109 paediatric patients aged 1 to 11 years with endoscopically proven GORD to evaluate safety and tolerability of NEXIUM once daily for up to eight weeks. Dosing of patients was based on weight with patients weighing <20 kg receiving esomeprazole 5 mg or 10 mg once daily and patients weighing ≥20 kg receiving esomeprazole 10 mg or 20 mg once daily. Fifty-three patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 40 (88.9%) of these patients had their erosive oesophagitis healed through eight weeks. A statistically significant reduction in overall GORD symptom scores from baseline to the final visit, as assessed by the physician/investigators, was observed in all treatment groups. In addition a statistically significant reduction in symptoms from baseline was observed at each study visit

(Week 2, Week 4, Week 6, and final visit) for all treatment groups ($p < 0.0036$). Adverse reactions recorded during the study did not identify any new safety concerns.

On demand treatment

Three large randomised long-term placebo controlled double-blind clinical trials in patients with non-erosive GORD were evaluated to assess the efficacy of on-demand treatment with esomeprazole 20 mg and/or 40 mg or placebo over a 6 month period following initial complete resolution of heartburn.

Based on the primary variable of “time to study discontinuation due to unwillingness to continue” there was no difference between esomeprazole 20 mg and 40 mg. Following initial treatment, effective symptom control is maintained in approximately 90% of patients taking on demand therapy with either esomeprazole 20 mg or 40 mg once daily, when needed. On average, patients only took one dose of esomeprazole approximately every 3 days to effectively control their symptoms, and most patients took esomeprazole for 3 consecutive days or less.

Short-term treatment of NSAID associated upper gastrointestinal (GI) symptoms

Two large randomised multicentre placebo controlled double-blind trials (NEN-0001; $n=402$ and NEN-0003; $n=376$) were evaluated to assess the efficacy of esomeprazole 20 mg orally versus placebo through 4 weeks of treatment of upper GI symptoms associated with NSAID use in patients receiving daily NSAID (non-selective and COX-2 selective) therapy.

The primary endpoint for both trials was change in severity of upper GI symptoms associated with NSAID use (pain, discomfort, or burning in the upper abdomen) referred to as upper GI symptoms. Patients completed a diary card once daily during the study period and were instructed to fill in the diary card at the same time each day throughout the study, close to intake of study drug. The patient was asked to rate the intensity of his/her upper GI symptoms by the following question: “How severe has your most intense episode of pain, discomfort or burning in the upper abdomen been during the last 24 hours?” The question was answered using a 7-graded scale as follows: 0=None (No symptoms); 1=Minimal (Can be easily ignored without effort); 2=Mild (Can be ignored with effort); 3=Moderate (Cannot be ignored but does not influence my daily activities); 4=Moderately Severe (Cannot be ignored and occasionally limits my daily activities); 5=Severe (Cannot be ignored and often limits my daily activities); 6=Very Severe (Cannot be ignored and markedly limits my daily activities and often requires rest). Additional symptoms (heartburn, acid regurgitation, and abdominal bloating, and nausea) were captured by investigator-recorded assessments and were considered to be supportive of the primary study endpoint. A further analysis was performed for; age; gender; race; *H. pylori* status; NSAID compliance and baseline NSAID type. Validated patient-reported outcome (PRO) measures (including a disease-specific health related quality-of-life questionnaire Gastrointestinal Symptom Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD)) were also selected as secondary endpoints.

In both trials, NEXIUM was significantly better than placebo in the treatment of upper GI symptoms (pain, discomfort and burning in the upper abdomen) in patients using non-selective or COX-2-selective NSAIDs (see Table 11). These differences were evident at 2 weeks and were sustained or further improved after 4 weeks of treatment. The median time for patients to achieve relief of upper GI symptoms for NEXIUM 20 mg was 10 to 11 days

compared to 17 to 21 days for placebo, across both trials. The NEXIUM 20 mg group gained a significantly higher percentage of symptom-free days (range 29.0% to 30.6% of days) compared to placebo (range 13.9 % to 21.0 % of days) and gained significantly better resolution of investigator-recorded symptoms of heartburn and acid regurgitation compared to placebo.

Table 11 **Difference between esomeprazole and placebo in mean change in the upper GI symptom score from the last 7 days in the run-in-period to the last 7 days.**

	NEN-0001	NEN-0003
Statistic	E20 vs placebo	E20 vs placebo
Estimated mean difference*	-0.59	-0.61
95% CI	-0.86, -0.32	-0.86, -0.36
p-value	<0.0001	<0.0001

* a difference of 0.4 units on a 7-graded scale is considered clinically important

Based on the Quality of Life in Reflux and Dyspepsia questionnaire, patients on NEXIUM 20 mg gained significantly improved well-being (emotional distress dimension), sleep quality (sleep problem dimension) and improved ability to eat and drink (food/drink problems dimension) compared to placebo. The GSRS questionnaire indicated significantly less reflux symptoms in both studies and significantly less abdominal pain and indigestion in one of the two studies.

No dosage adjustment is required based on age category, gender, race, or type of NSAID. Efficacy parameters were not affected by *H. pylori* status.

Gastric ulcer healing

Two large randomised, multicentre, active-controlled, comparative, double-blind, parallel-group trials were conducted to assess the efficacy of esomeprazole 40 mg and 20 mg once daily versus ranitidine 150 mg twice daily through 8 weeks of treatment for healing of gastric ulcers in patients receiving daily NSAID (non- selective and COX-2 selective) therapy. Patients had at least one gastric ulcer of ≥ 5 mm but not > 25 mm at greatest diameter. The primary variable was the gastric healing status (healed or unhealed) as observed endoscopically through 8 weeks.

A total of 846 patients were randomised (SH-NEN-0005 n=406; SH-NEN-0006 n=440); 765 patients completed the studies.

In SH-NEN-0005, the efficacy evaluation based on the ITT population (n=399) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at both Week 4 (E40 p=0.036, E20 p=0.023) and Week 8 (E40 p=<0.001, E20 p=0.003) compared to the ranitidine 150 mg twice daily treatment. The Week 8 results in the PP population (n=301) were similar to those in the ITT population. In addition, esomeprazole treatment resulted in a statistically significant greater beneficial effect on some patient-reported and investigator-assessed NSAID-associated upper GI symptoms compared to ranitidine following 8 weeks of treatment.

In SH-NEN-0006, the efficacy evaluation based on the ITT population (n=410) demonstrated that esomeprazole 40 mg and esomeprazole 20 mg treatment resulted in statistically significant higher observed gastric ulcer healing rates at Week 4 compared to the ranitidine 150 mg twice daily treatment (E40 p=0.009, E20 p=0.003). At week 8, although not statistically different, the healing rates were numerically higher with esomeprazole 40 mg and esomeprazole 20 mg compared to ranitidine 150 mg twice daily. The Week 4 and Week 8 results in the PP population were similar to those in the ITT population.

Ulcer prevention

Two large randomised, multicentre, placebo-controlled, double-blind, parallel-group studies were conducted to assess the efficacy of up to 6 months of treatment with esomeprazole 40 mg and 20 mg once daily versus placebo in preventing gastric ulcers and/or duodenal ulcers in patients receiving continuous NSAID (non-selective and COX-2 selective) therapy, who were at risk of developing NSAID related ulcers.

A total of 1429 patients were randomised (SH-NEN-0013 n=585; SH-NEN-0014 n=844); 1067 patients completed the studies.

Patients enrolled in the studies were ulcer free (as determined by endoscopy at baseline; erosions were permitted) but at risk of developing NSAID-associated gastric ulcers and/or duodenal ulcers because of a documented gastric and duodenal ulcer within the past 5 years and/or age ≥ 60 years.

The cumulative proportion of patients without gastric ulcer and/or duodenal ulcer throughout the 6 month treatment period was higher in patients treated with esomeprazole 40 mg or esomeprazole 20 mg than in patients treated with placebo. The reduction of gastric ulcer and/or duodenal ulcer development relative to placebo was statistically significant in the 2 studies, both in the ITT and PP population.

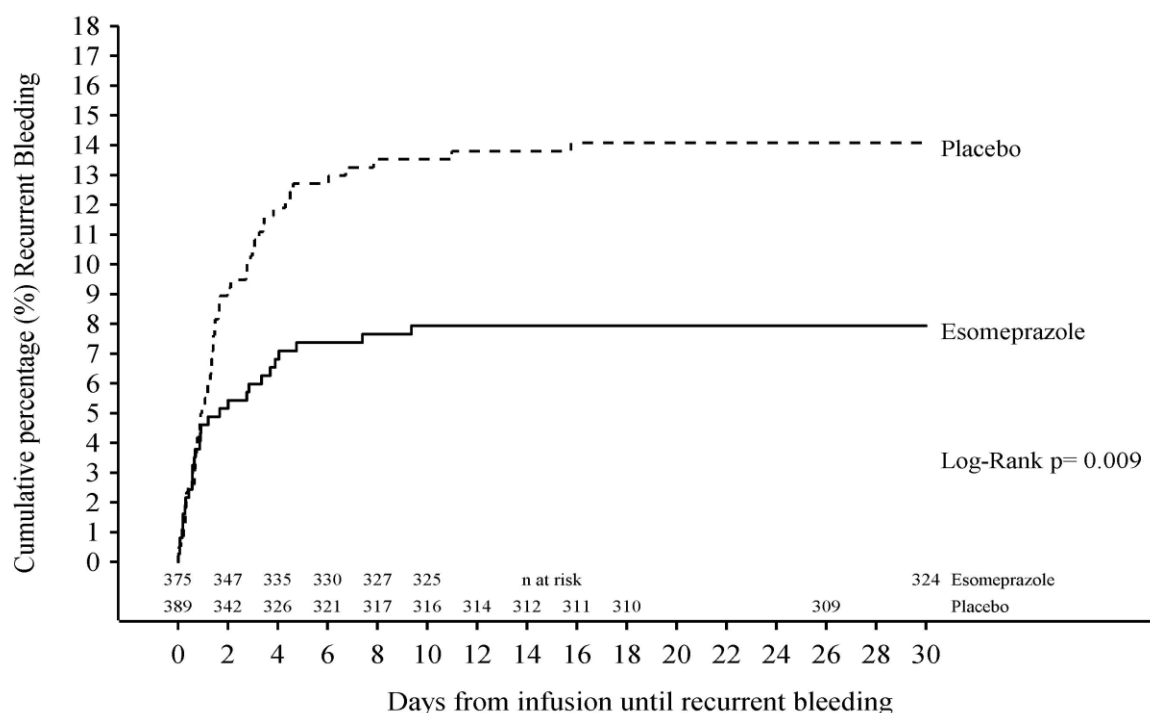
A 26-week randomised double-blind, placebo-controlled trial (n=992) was conducted to evaluate the efficacy of esomeprazole 20 mg daily for the prevention of gastric and/or duodenal ulcers in patients taking low-dose aspirin (75-325 mg daily) at moderate to high risk of developing gastroduodenal ulcers. In patients receiving esomeprazole 20 mg the estimated cumulative proportion of patients with a gastric and/or duodenal ulcer at 6 months was significantly lower compared to the placebo group (1.8% vs 6.2%, p=0.0007, life-table analysis). Esomeprazole 20 mg daily was also significantly more effective at reducing the risk of lesions in the oesophagus compared to placebo in patients using low dose aspirin.

Prevention of rebleeding of gastric or duodenal ulcers

In a randomised, double blind, placebo-controlled clinical study, 764 patients with bleeding gastric or duodenal ulcers were randomised to receive NEXIUM IV for Injection (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg NEXIUM IV administered as a bolus infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hrs. After the initial 72 hour period, all patients received oral NEXIUM 40 mg for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the NEXIUM IV treated group compared to 10.3% for the placebo group. At 7 and 30 days post-treatment, the occurrence of rebleeding in the NEXIUM treated group versus the placebo treated group was 7.2% vs 12.9% and 7.7% vs

13.6% respectively. The Kaplan-Meier curve in Fig 1 shows the cumulative percentage of patients rebleeding within 30 days of commencing treatment.

Figure 1 **Kaplan-Meier estimate of the cumulative percentage of patients with rebleeding within 30 days (iv+oral treatment)**



NEXIUM IV treatment followed by the oral treatment regimen reduced the total number of days patients were hospitalised due to rebleeding during the 30 day treatment by 43% compared to placebo. Hospitalisations exceeding 5 days were observed in 4.8% of patients treated with NEXIUM compared to 10.5% for placebo.

Control of gastric acid secretion in patients with hypersecretory states

A 12 month study in 21 patients diagnosed with pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion was conducted to determine if appropriately titrated doses of esomeprazole controlled gastric acid secretion (pharmacodynamic assessment) during the study and to evaluate the safety and tolerability of esomeprazole in patients with hypersecretory states. Basal acid output was controlled with high-dose esomeprazole (doses from 40 mg bid up to 240 mg daily) in 95% (20) of patients at 6 months and 90% (19) at 12 months. Most patients achieved control on 40 mg bid. High-dose esomeprazole was found to be generally safe and well tolerated throughout the study.

Helicobacter pylori eradication

Two large randomised double-blind clinical trials were evaluated to assess the efficacy of esomeprazole in combination with specified antibiotics for the eradication of *H. pylori*. In the first trial, study B13, the seven day regimen consisted of esomeprazole 20 mg bid in combination with amoxicillin, 1000 mg bid and clarithromycin 250 mg x 2 bid (EAC) and was compared with standard seven day therapy of omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 250 mg x 2 bid (OAC). In the second trial, study B14, the above seven day treatment regimen was combined with three additional weeks of treatment with

placebo (EAC + placebo) or omeprazole (OAC + omeprazole). This study looked at the healing rate of duodenal ulcer and eradication rate of *H. pylori* following treatment with omeprazole or placebo.

The estimated intention to treat (ITT) eradication rates in study B13 for the EAC and OAC treatment groups were 90% and 88% respectively. In study B14 the estimated ITT cumulative healing rates were 97% and 96% in the EAC + placebo and OAC + omeprazole groups, respectively, whilst the estimated ITT eradication rates were 86% and 88% respectively

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets or enteric coated granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an

inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m² basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H₂-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The 20 mg and 40 mg tablets are coloured with titanium dioxide and iron oxide red CI77491. In the 20 mg tablet iron oxide yellow CI77492 is also added.

Each sachet of granules for oral suspension contains the following inactive ingredients: glyceryl monostearate, hypromellose, hypromellose, magnesium stearate, methacrylic acid

copolymer, polysorbate 80, talc, triethyl citrate, glucose, xanthan gum, crospovidone, citric acid, iron oxide yellow and sugar spheres (maize starch and sucrose).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

NEXIUM granules for oral suspension are available in cartons containing 30 unit dose sachets.

NEXIUM tablets are available in wallets (containing blisters); blister packs of 7, 15[#], 30, and 100[#] tablets.

[#]non-marketed pack size

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

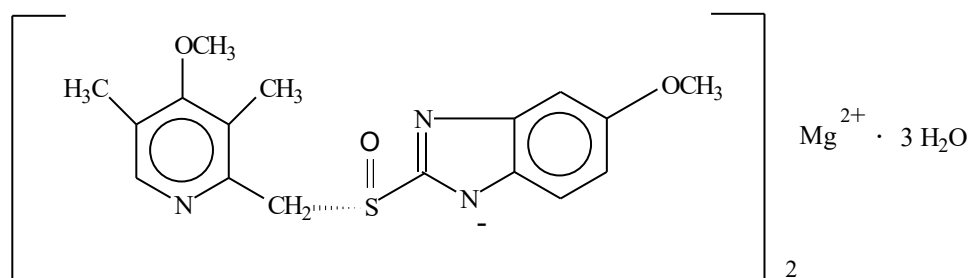
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number

217087-09-7

Molecular formula $C_{34}H_{36}N_6O_6S_2Mg \cdot 3H_2O$ **Molecular weight**

767.2 (trihydrate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
 ABN 54 009 682 311
 66 Talavera Road
 Macquarie Park NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

22 December 2010

10. DATE OF REVISION

3 January 2025

Summary table of changes

Section changed	Summary of new information
All	Incorporated PI into current template
4.4	Updated under “Acute tubulointerstitial nephritis” to replace “acute interstitial nephritis” with “acute tubulointerstitial nephritis” and added the sentence “Acute tubulointerstitial nephritis can progress to renal failure”.
4.8	Updated adverse effect under Renal and urinary disorders to “Very Rare: tubulointerstitial nephritis (with possible progression to renal failure)”.
5.1	Added missing heading to Table 6.
6.5	Removed details on 100-tablet bottle pack.

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VV-RIM-01376008 v22.0

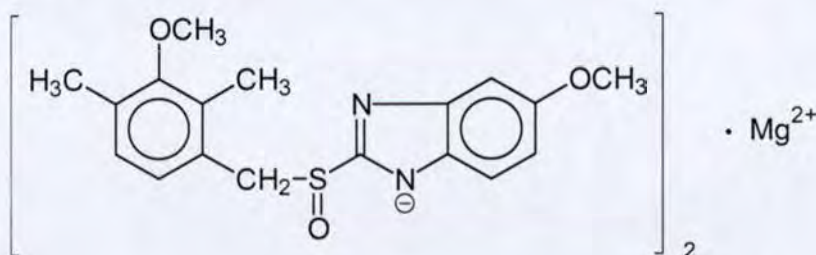
Pages 1-5 and 20-245 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

LOSEC® TABLETS
Multiple Unit Pellet System
PRODUCT INFORMATION
(omeprazole magnesium)

NAME OF DRUG

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS Number: 95382-33-5
Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg$
Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methylacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres. The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once-daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion. (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric-coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

Clinical Trials

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference		
				%	95% CI	
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

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untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5 – 17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1 – 17 years, oral omeprazole 0.5 – 0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD
The relief of heartburn and other symptoms associated with GORD.
2. Erosive oesophagitis
The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

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CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium or any other ingredients.

PRECAUTIONS

As with all antsecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78 week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL-cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in Pregnancy Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

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Use in Lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER DRUGS

Absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Theoretical interactions

Ketoconazole, Itraconazole

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease during treatment with omeprazole.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Demonstrated interactions

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54 % and the mean elimination half life of diazepam was increased by 130 %, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20 % and increased the elimination half life by 27 %. It is recommended that plasma concentration of phenytoin be monitored in patients co-prescribed LOSEC 40 mg and phenytoin. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

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Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

It is recommended that coagulation tests be monitored closely when initiating or ceasing LOSEC Tablets in patients co-prescribed warfarin.

Atazanavir

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Demonstrated interactions

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

ADVERSE REACTIONS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Gastrointestinal

Common	diarrhoea, constipation, abdominal pain, nausea/vomiting, flatulence
*Rare	stomatitis, gastrointestinal candidiasis and dry mouth
Very rare	dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Central and peripheral nervous system

Common	headache
Uncommon	dizziness, paraesthesia, somnolence, insomnia, vertigo
Rare	reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients

Hepatic

Uncommon	increased liver enzymes
Rare	encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure

Skin

Uncommon	rash, urticaria and/or pruritus
Rare	photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia

Other

Uncommon	malaise
Rare	hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis, anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.
Very rare	impaired renal function, including nephrosis, dyspnoea, weight increase and hypokalaemia (reported in children)

Endocrine

Rare	gynaecomastia
Very rare	impotence (although causality has not been established)

Haematological

Rare	leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
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Musculoskeletal

Rare	arthralgia, muscular weakness and myalgia
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DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing

occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10 - 20 kg	Losec Tablets 10 mg once daily for 2 to 8 weeks
> 20 kg	Losec Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transit, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and

no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

Losec is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 11th September 2002

Date of most recent amendment: 2nd December 2005

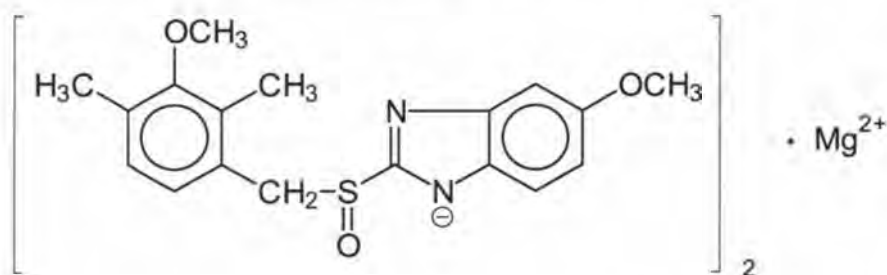
Pages 1-210 and 225-285 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

LOSEC® TABLETS
Multiple Unit Pellet System
PRODUCT INFORMATION
(omeprazole magnesium)

NAME OF DRUG

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS Number: 95382-33-5
 Molecular formula: C₃₄H₃₆N₆O₆S₂Mg
 Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methylacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres. The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once-daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion. (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric-coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

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Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

Clinical Trials

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference		
				%	95% CI	
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with

untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5 – 17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1 – 17 years, oral omeprazole 0.5 – 0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD
The relief of heartburn and other symptoms associated with GORD.
2. Erosive oesophagitis
The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium or any other ingredients.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78 week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL-cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in Pregnancy Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in Lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER DRUGS

Absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Theoretical interactions

Ketoconazole, Itraconazole

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease during treatment with omeprazole.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Demonstrated interactions

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54 % and the mean elimination half life of diazepam was increased by 130 %, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20 % and increased the elimination half life by 27 %. ~~It is recommended that plasma concentration of phenytoin be monitored in patients co-prescribed LOSEC 40 mg and phenytoin~~ Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

~~It is recommended that coagulation tests be monitored closely when initiating or ceasing LOSEC Tablets in patients co-prescribed warfarin.~~ In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Atazanavir

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Demonstrated interactions

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

ADVERSE REACTIONS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Gastrointestinal

Common	diarrhoea, constipation, abdominal pain, nausea/vomiting, flatulence
*Rare	stomatitis, gastrointestinal candidiasis and dry mouth
Very rare	dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Central and peripheral nervous system

Common	headache
Uncommon	dizziness, paraesthesia, somnolence, insomnia, vertigo
Rare	reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients

Hepatic

Uncommon	increased liver enzymes
Rare	encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure

<i>Skin</i>	
<i>Uncommon</i>	rash, urticaria and/or pruritus, <u>dermatitis</u>
<i>Rare</i>	photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia
<i>Other</i>	
<i>Uncommon</i>	malaise
<i>Rare</i>	hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis, anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.
<i>Very rare</i>	<i>impaired renal function, including nephrosis</i> , dyspnoea, weight increase and hypokalaemia (reported in children)
<i>Endocrine</i>	
<i>Rare</i>	gynaecomastia
<i>Very rare</i>	impotence (although causality has not been established)
<i>Haematological</i>	
<i>Rare</i>	leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
<i>Musculoskeletal</i>	
<i>Rare</i>	arthralgia, muscular weakness and myalgia

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10 - 20 kg	Losec Tablets 10 mg once daily for 2 to 8 weeks
> 20 kg	Losec Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transit, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]*not marketed*

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd

ABN 54 009 682 311

Alma Road

NORTH RYDE NSW 2113

Losec is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 11th September 2002

Date of most recent amendment: ~~2nd December 2005~~ 10th April 2006

Pages 1-188 and 204-206 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

LOSEC® TABLETS

Multiple Unit Pellet System

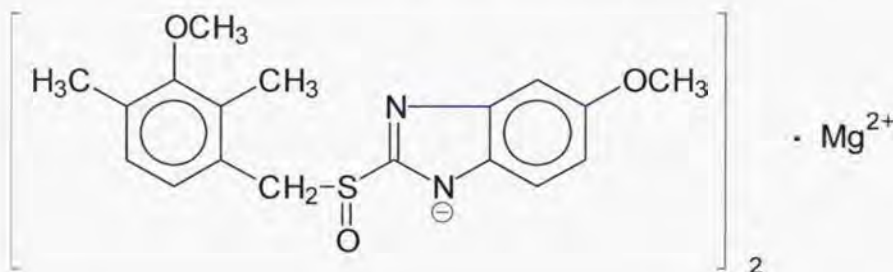
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE DRUG

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg$

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres. The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final

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step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

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Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

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CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium or any other ingredients.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Theoretical interactions

Ketoconazole, Itraconazole

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease during treatment with omeprazole.

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Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Demonstrated interactions

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum

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levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Demonstrated interactions

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

ADVERSE REACTIONS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Gastrointestinal

Common	diarrhoea, constipation, abdominal pain, nausea/vomiting, flatulence
Rare	stomatitis, gastrointestinal candidiasis and dry mouth
Very rare	dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Central and peripheral nervous system

Common	headache
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Uncommon	dizziness, paraesthesia, somnolence, insomnia, vertigo
Rare	reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients
<i>Hepatic</i>	
Uncommon	increased liver enzymes
Rare	encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure
<i>Skin</i>	
Uncommon	rash, urticaria and/or pruritus, dermatitis
Rare	photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia
<i>Other</i>	
Uncommon	malaise
Rare	hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis, anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.
Very rare	impaired renal function, including nephrosis, dyspnoea, weight increase and hypokalaemia (reported in children)
<i>Endocrine</i>	
Rare	gynaecomastia
Very rare	impotence (although causality has not been established)
<i>Haematological</i>	
Rare	leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
<i>Musculoskeletal</i>	
Rare	arthralgia, muscular weakness and myalgia

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within

30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing

occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness,

abdominal pain, diarrhoea and headache have been reported from overdose with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdose have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdose treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]*not marketed*

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

LOSEC is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 11th September 2002

Date of most recent amendment: 30 June 2008

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Pages 1-23 and 40-206 have been removed in accordance with section 22 of the FOI Act as they are irrelevant to the scope of this request.

LOSEC® TABLETS

Multiple Unit Pellet System

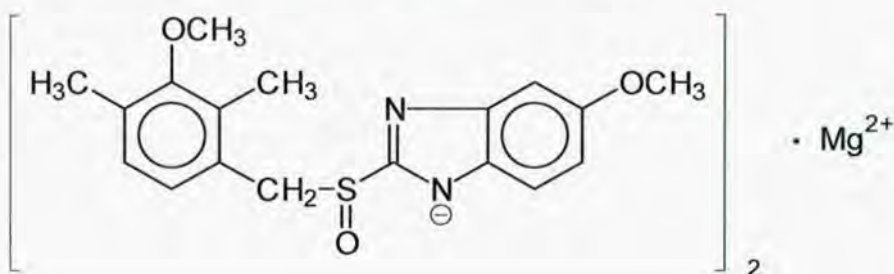
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE DRUG

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres. The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final

step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

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Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months,

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77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special Patient Populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Effects related to acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of

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gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus

forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Theoretical interactions

Ketoconazole, Itraconazole

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease during treatment with omeprazole.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Demonstrated interactions

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

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In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Demonstrated interactions

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

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Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

ADVERSE REACTIONS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Gastrointestinal

Common	diarrhoea, constipation, abdominal pain, nausea/vomiting, flatulence
Rare	stomatitis, gastrointestinal candidiasis and dry mouth
Very rare	dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Central and peripheral nervous system

Common	headache
Uncommon	dizziness, paraesthesia, somnolence, insomnia, vertigo
Rare	reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients

Hepatic

Uncommon	increased liver enzymes
Rare	encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure

Skin

Uncommon	rash, urticaria and/or pruritus, dermatitis
Rare	photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia

Other

Uncommon	malaise
Rare	hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis, anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.
Very rare	impaired renal function, including nephrosis, dyspnoea, weight increase and hypokalaemia (reported in children)

Endocrine

Rare	gynaecomastia
Very rare	impotence (although causality has not been established)

Haematological

Rare	leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
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Musculoskeletal

Rare	arthralgia, muscular weakness and myalgia
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DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during

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initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been

associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

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LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

LOSEC is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 11th September 2002

Date of most recent amendment: 25 November 2009

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LOSEC® TABLETS

Multiple Unit Pellet System

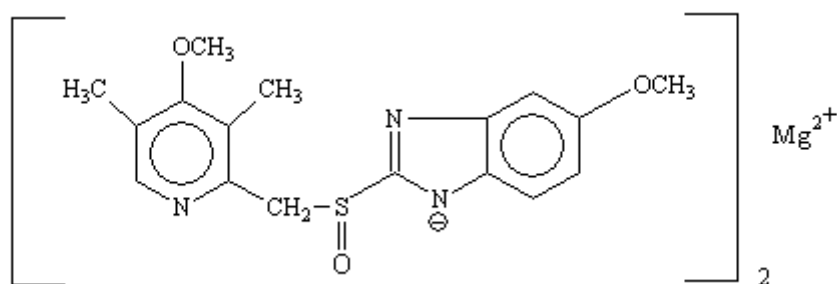
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE DRUG

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres. The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the

intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special Patient Populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of

20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Effects related to acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease and the absorption of digoxin can increase during treatment with omeprazole.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Demonstrated interactions

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Demonstrated interactions

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effect on Laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE REACTIONS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Gastrointestinal

Common	diarrhoea, constipation, abdominal pain, nausea/vomiting, flatulence
Rare	stomatitis, gastrointestinal candidiasis and dry mouth
Very rare	dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Central and peripheral nervous system

Common	headache
Uncommon	dizziness, paraesthesia, somnolence, insomnia, vertigo
Rare	reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients

Hepatic

Uncommon	increased liver enzymes
Rare	encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure

Skin

Uncommon	rash, urticaria and/or pruritus, dermatitis
Rare	photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia

Other

Uncommon	malaise
Rare	hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis, anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.
Very rare	impaired renal function, including nephrosis, dyspnoea, weight increase, hypomagnesaemia and hypokalaemia (reported in children)

Endocrine

Rare	gynaecomastia
Very rare	impotence (although causality has not been established)

Haematological

Rare	leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
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Musculoskeletal

Rare	arthralgia, muscular weakness and myalgia
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DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses

of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

LOSEC is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 11th September 2002

Date of most recent amendment: 3 June 2010

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LOSEC® TABLETS

Multiple Unit Pellet System

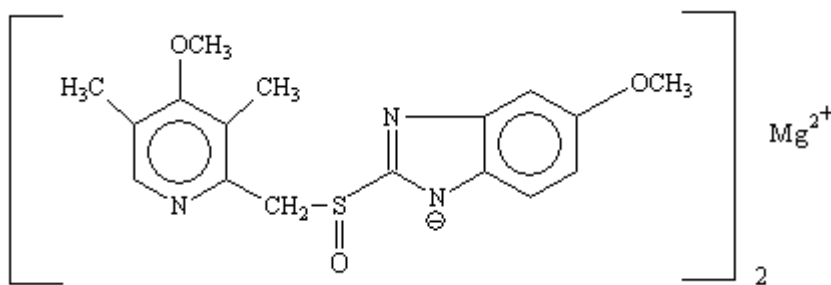
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the

intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-

AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (eg. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed Malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be

excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special Patient Populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were

associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease and the absorption of digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was

increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions eg. Fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children)

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

LOSEC is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 26 November 2010

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LOSEC® TABLETS

Multiple Unit Pellet System

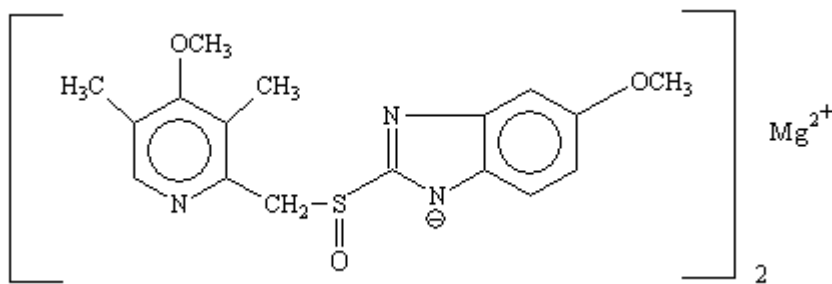
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the

intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-

AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (eg. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse

in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed Malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be

excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special Patient Populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were

associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease and the absorption of digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was

increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions eg. Fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children)

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

LOSEC is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 22 December 2010

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LOSEC® TABLETS

Multiple Unit Pellet System

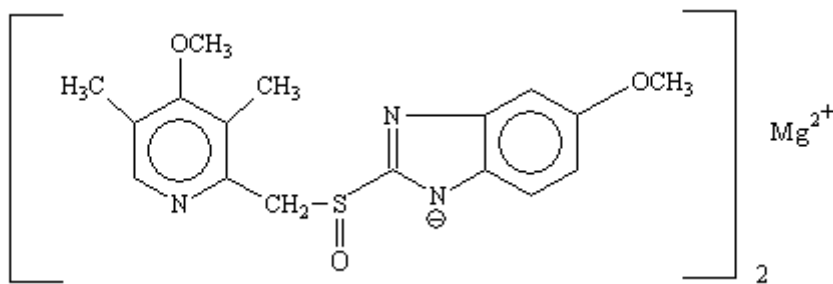
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: $\text{C}_{34}\text{H}_{36}\text{N}_6\text{O}_6\text{S}_2\text{Mg}$

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the

intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-

AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (eg. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse

in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed Malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be

excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special Patient Populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were

associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole etc, may decrease and the absorption of digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was

increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions eg. Fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children)

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

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LOSEC[®] TABLETS

Multiple Unit Pellet System

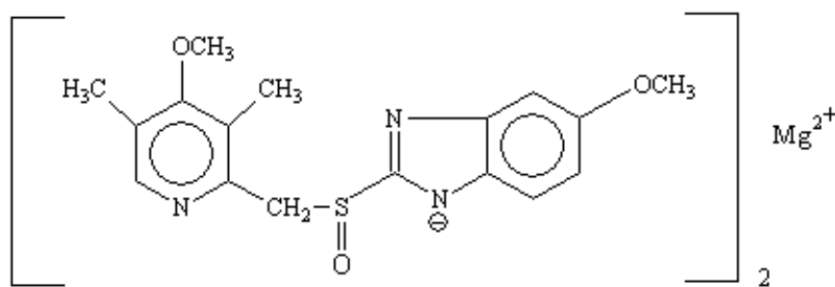
(omeprazole magnesium)

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC[®] is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the

intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-

AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (eg. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse

in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD
The relief of heartburn and other symptoms associated with GORD.
2. Erosive oesophagitis
The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed Malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be

excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special Patient Populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, Mutagenicity, Impairment of Fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were

associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH e.g. ketoconazole, itraconazole, erlotinib etc, may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are

via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions eg. Fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children)

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses

of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in Children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]*not marketed*

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

LOSEC is a trade mark of the AstraZeneca group of companies.

Date of TGA approval: 22 December 2010

Date of most recent amendment: 16 May 2011

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LOSEC® TABLETS

omeprazole magnesium

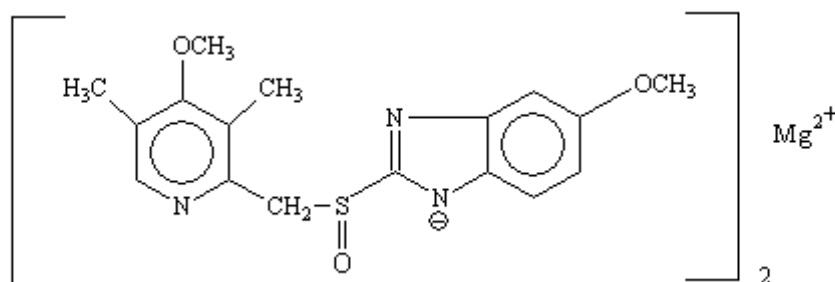
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC_{90} of 25 $\mu g/mL$ against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see PRECAUTIONS). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

Interactions with other medicines

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Contraindications).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel and omeprazole resulting in a decreased exposure of the active metabolite of clopidogrel and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation. The clinical relevance of this interaction is uncertain. Concomitant use of omeprazole and clopidogrel should be avoided.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or

- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

Storage

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE DRUG

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

Date of TGA approval: 22 December 2010

Date of most recent amendment: 10 April 2014

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LOSEC® TABLETS

omeprazole magnesium

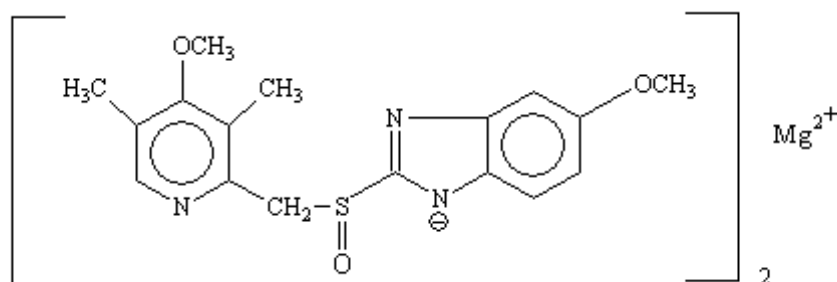
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin hard, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of

gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on

any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdose with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdose with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdose have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdose treatment should be supportive and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]*not marketed*

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 December 1998

DATE OF MOST RECENT AMENDMENT

5 June 2014

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LOSEC® TABLETS

omeprazole magnesium

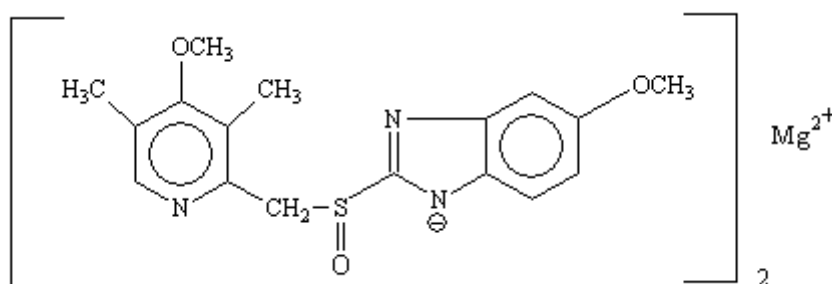
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red C177491 and/or iron oxide yellow C177492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of

gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold

anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant

treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in

association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]*not marketed*

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS (THE ARTG)**

14 December 1998

DATE OF MOST RECENT AMENDMENT

1 December 2014

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LOSEC® TABLETS

omeprazole magnesium

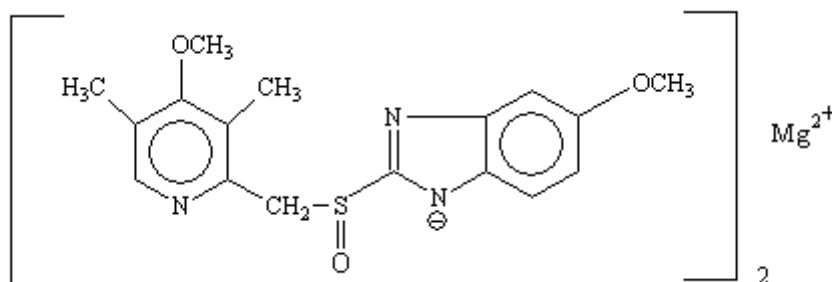
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red C177491 and/or iron oxide yellow C177492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of

clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 December 1998

DATE OF MOST RECENT AMENDMENT

1 June 2015

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LOSEC® TABLETS

omeprazole magnesium

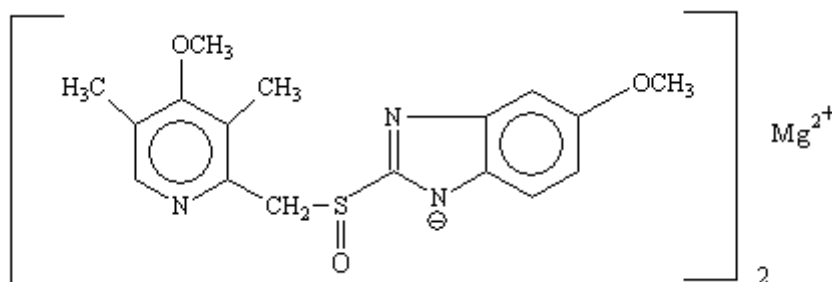
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red C177491 and/or iron oxide yellow C177492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.

2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.

3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.

4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.

5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these

individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.

- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations.

For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets

disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxycillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxycillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been

reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdose treatment should be supportive and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 December 1998

DATE OF MOST RECENT AMENDMENT

6 July 2015

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LOSEC® TABLETS

omeprazole magnesium

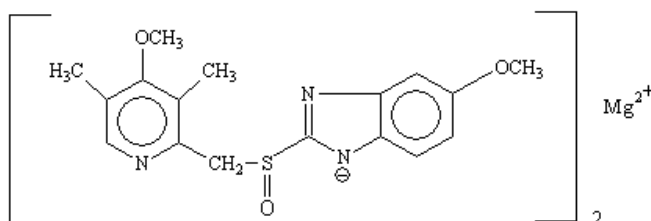
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red C177491 and/or iron oxide yellow C177492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final

step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g.

the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on

these data, concomitant use of omeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of

clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 December 1998

DATE OF MOST RECENT AMENDMENT

23 March 2016

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LOSEC® TABLETS

omeprazole magnesium

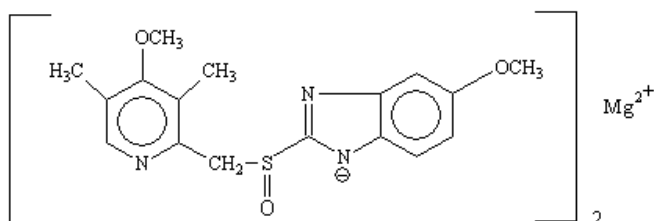
Multiple Unit Pellet System

PRODUCT INFORMATION

NAME OF THE MEDICINE

LOSEC® is a proton pump inhibitor. The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. The chemical name is di-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number: 95382-33-5

Molecular formula: C₃₄H₃₆N₆O₆S₂Mg

Molecular weight: 713.1

DESCRIPTION

LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient with glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final

step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Pharmacokinetics

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g.

the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

CLINICAL TRIALS

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

3. Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on

these data, concomitant use of omeprazole and clopidogrel should be avoided (see **INTERACTIONS WITH OTHER MEDICINES**).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Hepatic insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg omeprazole daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Carcinogenicity, mutagenicity, impairment of fertility

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

Effects on ability to drive and operate machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Metabolism

Cytochrome P-450 effects

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of

clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

DOSAGE AND ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks
>20 kg	LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Geriatrics

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

LOSEC® Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

30 tablets are provided in a blister pack. The tablets should be dispensed and stored in the original container.

LOSEC Tablets 10 mg, 20 mg and 40 mg[#]: stored below 25°C.

[#]not marketed

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 December 1998

DATE OF MOST RECENT AMENDMENT

18 December 2017

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AUSTRALIAN PRODUCT INFORMATION

LOSEC® TABLETS

omeprazole magnesium

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

[#]not marketed

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks

>20 kg LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any

point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg

omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be

necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single

cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it.

The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150

mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12–60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g.

the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red C177491 and/or iron oxide yellow C177492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

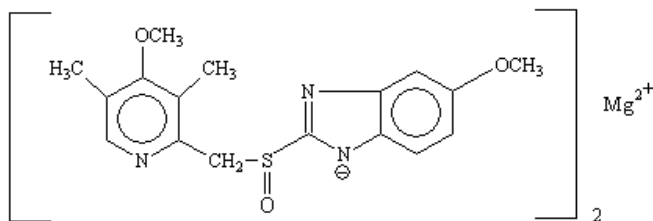
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is

a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

C₃₄H₃₆N₆O₆S₂Mg

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
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66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

14 March 2019

Summary table of changes

Section changed	Summary of new information
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Section changed	Summary of new information
All sections	PI reformatted
4.4	New precaution – subacute cutaneous lupus erythematosus

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AUSTRALIAN PRODUCT INFORMATION

LOSEC® TABLETS

omeprazole magnesium

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

[#]not marketed

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks

>20 kg LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any

point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg

omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be

necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness,

abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in

patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12–60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g.

the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red C177491 and/or iron oxide yellow C177492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

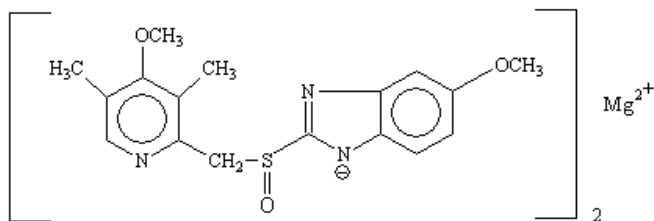
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is

a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

C₃₄H₃₆N₆O₆S₂Mg

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

AstraZeneca Pty Ltd
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MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

5 July 2019

Summary table of changes

Section changed	Summary of new information
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Section changed	Summary of new information
4.8	New adverse effect – rebound acid hypersecretion upon discontinuation of long-term PPI therapy

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AUSTRALIAN PRODUCT INFORMATION

LOSEC[®] TABLETS

omeprazole magnesium

Multiple Unit Pellet System

1. NAME OF THE MEDICINE

Omeprazole magnesium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in LOSEC Tablets is omeprazole magnesium, a substituted benzimidazole. LOSEC is available in 10 mg, 20 mg and 40 mg tablets containing omeprazole magnesium 10.3 mg, 20.6 mg and 41.3 mg, respectively, as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

LOSEC Tablets 10 mg are a light pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 10 mg on the other. Each tablet contains omeprazole magnesium 10.3 mg as enteric-coated pellets.

LOSEC Tablets 20 mg are a pink, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 20 mg on the other. Each tablet contains omeprazole magnesium 20.6 mg as enteric-coated pellets.

LOSEC Tablets 40 mg[#] are a red-brown, oblong, biconvex, film-coated tablet engraved with the LOSEC logo on one side and 40 mg and a score on the other. Each tablet contains omeprazole magnesium 41.3 mg as the enteric-coated pellets.

[#]*not marketed*

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LOSEC Tablets are indicated for:

Gastro-Oesophageal Reflux Disease (GORD)

1. Symptomatic GORD

The relief of heartburn and other symptoms associated with GORD.

2. Erosive oesophagitis

The treatment and prevention of relapse.

Peptic Ulcers

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
5. Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly, or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

LOSEC Tablets should be swallowed whole (not broken or chewed) with liquid.

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable) or non-carbonated fruit juices. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Symptomatic GORD

Recommended dose for symptom relief: LOSEC Tablets 10 mg to 20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with LOSEC Tablets 20 mg daily, further investigation is recommended.

Erosive oesophagitis

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

It is recommended that, after healing, maintenance therapy be commenced, LOSEC Tablets 10 mg once daily. If needed, this dose should be increased to LOSEC Tablets 20 mg once daily.

Peptic ulcer disease associated with *Helicobacter pylori* infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both three times a day, for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease see further dosage recommendations for duodenal and gastric ulcer.

Duodenal ulcer

Recommended healing dosage: LOSEC Tablets 20 mg orally once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 4 to 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 10 mg to 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

Gastric ulcer

Recommended healing dosage: LOSEC Tablets 20 mg once daily for 4 to 8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, LOSEC Tablets 40 mg once daily usually produces healing within 8 weeks.

Maintenance therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is LOSEC Tablets 20 mg daily.

For NSAID-associated duodenal ulcers see NSAID-associated gastroduodenal lesions.

NSAID-associated gastric or duodenal ulcers or erosions

In patients with or without continued NSAID treatment, the recommended dose is LOSEC Tablets 20 mg to 40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is LOSEC Tablets 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: LOSEC Tablets 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20-120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in children

For use in children one year and older the recommended dose is:

<i>Weight</i>	<i>Dose</i>
10-20 kg	LOSEC Tablets 10 mg once daily for 2 to 8 weeks

>20 kg LOSEC Tablets 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

The tablet may be dispersed in yoghurt or orange juice to assist with administration.

Elderly

No dosage adjustment of LOSEC Tablets is necessary in the elderly.

Hepatic impairment

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of 20 mg omeprazole daily and no adjustment to the normal dosage regime is required (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

4.3 CONTRAINDICATIONS

Hypersensitivity to omeprazole magnesium, substituted benzimidazoles or any other ingredients.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Undiagnosed malignancy

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acute interstitial nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any

point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Cyanocobalamin (vitamin B-12) deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Osteoporotic fractures

Some published case controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Antimicrobial resistance

The development of antimicrobial resistance may have an adverse affect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Effects of acid inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping LOSEC. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Special patient populations

Use in hepatic impairment

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged indicating no accumulation of omeprazole or its metabolites. The normal dose of 20 mg

omeprazole daily may be used in patients with severe liver disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.

Effects on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of omeprazole on other drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage, when LOSEC Tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for 7 days reduced plasma clearance of IV phenytoin by 15-20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be

necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin. Plasma concentrations of the more potent S-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH (e.g. ketoconazole, itraconazole, erlotinib etc) may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Effects of other drugs on omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Potential interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20-40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofoetal toxicity.

Use in pregnancy – Category B3

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC. In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring *postpartum* growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

LOSEC Tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions (e.g. fever, angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: Blurred vision

Ear and Labyrinth disorders

Uncommon: Vertigo

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritis, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)

Not known: Subacute cutaneous lupus erythematosus (SCLE)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Very rare: Impaired renal function, including nephrosis

Reproductive system and breast disorders

Rare: Gynaecomastia

Very rare: Impotence (although causality has not been established)

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg omeprazole

(120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdose with omeprazole. Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdose have been transient, and no serious clinical outcome due to omeprazole has been reported. The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed. In suspected cases of overdose treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LOSEC is a proton pump inhibitor. Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+ , K^+ -ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose-dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on gastric acid secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin-stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3 to 5 days.

Peptic ulcer disease associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In vitro testing has shown that omeprazole has an MIC₉₀ of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agent results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other effects related to acid inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

Clinical trials

Gastro-Oesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo.

The % patients with complete relief of heartburn after 4 weeks is presented below.

Study	Group	N	Relief (% patients)	Group Difference	%	95% CI
Lind	Plac	105	13	Ome 10- Plac	18	9, 27
	Ome 10	199	31	Ome 20 - Plac	33	23, 43
	Ome 20	205	46	Ome 20 - Ome 10	15	6, 25
Venables	Ranit	135	36	Ome 10 - Ranit	0.2	-12, 12
	Ome 10	126	36	Ome 20 - Ranit	3.7	-8, 15
	Ome 20	130	39	Ome 20 - Ome 10	3.5	-8, 15
Bate	Plac	58	22	Ome 20 - Plac	36	17, 55
	Ome 20	48	58			

Plac= placebo; Ome= omeprazole; Ranit = ranitidine

Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n=1674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in

patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg bd or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of 5 of the clinical trials (n=1154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n=327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first three months of maintenance treatment were then healed and treated with a maintenance dose of 20 mg omeprazole. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from 7 controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). This involved a total of 1128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6-12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL-cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

Use in Children

In a trial in 65 children aged 0.5–17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12-60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1–17 years, oral omeprazole 0.5–0.6 mg/kg/day for 8 weeks achieved endoscopic healing in 2 children with giant gastric ulcer, 6 children with duodenal ulcer and 4 out of 5 children with oesophagitis.

There are no data on the use of omeprazole in children with less severe gastro-oesophageal reflux disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Omeprazole magnesium is acid labile and is administered orally as enteric coated granules in tablets. The enteric coating film, protecting the omeprazole magnesium, dissolves at a pH above 5.5. Hence omeprazole magnesium is not released until the pellets are emptied into the duodenum.

Once omeprazole magnesium dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of LOSEC Tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone.

Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during repeated dosing.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g.

the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Pharmacokinetics in children

Available data from children (≥ 1 year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects were markedly higher in female rats.

The same effects were seen in an additional 2-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL-cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL-cells following treatment for one month.
- b) H₂-receptor antagonists. In rats administered 2 g/kg/day of ranitidine in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.

- c) Surgical resection of the acid producing oxyntic mucosa. In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL-cell carcinoids during the 124 week study.

These findings show that the development of ECL-cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL-cell.

Omeprazole may also affect other cells in the gastrointestinal tract (for example, G cells) either directly or by inducing sustained hypochlorhydria but this possibility has not been extensively studied.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOSEC tablets contain the following inactive ingredients: glyceryl monostearate, hypolose, hypromellose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone, sodium stearyl fumarate, purified talc, titanium dioxide, triethyl citrate, sodium hydroxide and sugar spheres (maize starch and sucrose). The tablet is coloured with iron oxide red CI77491 and/or iron oxide yellow CI77492.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LOSEC is provided in blister packs containing 30 tablets. The tablets should be dispensed and stored in the original container.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

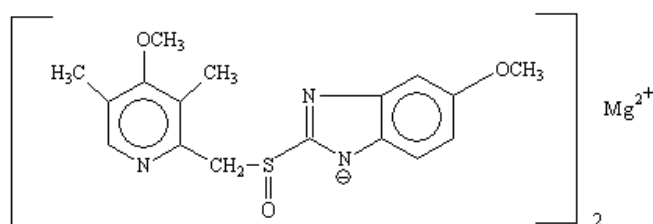
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium is

a crystalline substance which is freely soluble in methanol and slightly soluble in water.

The chemical structure of omeprazole magnesium is:



CAS number

95382-33-5

Molecular formula

C₃₄H₃₆N₆O₆S₂Mg

Molecular weight

713.1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

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Suite 1A, Level 2, 802 Pacific Highway
GORDON NSW 2072

Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

14 December 1998

10. DATE OF REVISION

03 November 2021

Summary table of changes

Section changed	Summary of new information
8	Transfer of sponsor