ZOTON® FasTabs 15 mg and 30 mg tablets

PRODUCT INFORMATION

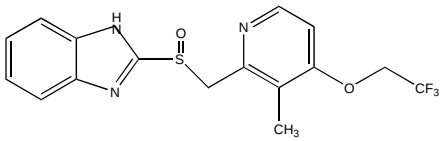
NAME OF THE MEDICINE

Lansoprazole

Chemical Name and Structure

2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

CAS No. 103577-45-3.



$C_{16}H_{14}F_3N_30_2S$ MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8°C with decomposition and has a pKa of 8.8.

Inactive ingredients:

Gastro-resistant microgranules: Lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).
Other excipients: crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Actions

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was ≤30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p\leq0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p <0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88 % with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months					
Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * (p≤0.001) versus lansoprazole 15 mg and 30 mg; # (p≤0.001) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*(p≤0.001) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime
NT = Night-time
H = Heartburn
EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer. Patients whose gastric or duodenal ulcer 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.
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).

6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age.

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors or any of the excipients in the tablets.
Severe hepatic impairment.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an in vivo assay of chromosomal damage. In vitro assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in foetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe

hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Interactions with other medicines

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs phenytoin (single IV doses only) and diazepam have been found.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs is strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis: 30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer: 30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer: 30 mg lansoprazole once daily for 8 weeks.

Acid-related dyspepsia: Lansoprazole 15 mg or 30 mg once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of *H. pylori*: The following combinations have been shown to be effective when used for 7 days:

- Lansoprazole 30 mg twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION

Zoton FasTabs 15 mg and 30 mg tablets

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Zoton FasTabs are supplied in blister packs of 7 or 28 tablets.

Storage

Store below 25°C.

Poison Schedule

S4, PRESCRIPTION ONLY MEDICINE.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114

Date of TGA Approval: 7 January 2009

Date of most recent amendment: 23 June 2011

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Proprietor of the Trademark Zoton®

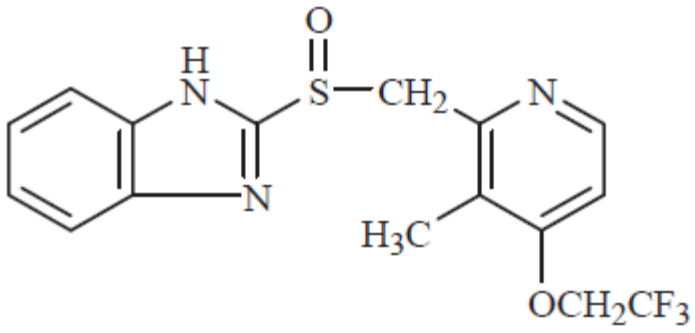
PRODUCT INFORMATION

ZOTON® FasTabs, Capsules and Granules for Suspension

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8°C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole and the following inactive ingredients:

Gastro-resistant microgranules: Lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients: crospovidone, magnesium stearate, strawberry flavour and aspartame.

These tablets are supplied in blister packs of 7 or 28 tablets.Zoton capsules contain 15 mg or 30 mg of lansoprazole and the following inactive ingredients:

Magnesium carbonate, sucrose, starch-maize, hydroxypropylcellulose, methacrylic acid copolymer, talc, macrogol 8000, titanium dioxide, polysorbate 80, colloidal anhydrous silica, erythrosine and indigo carmine (30mg capsule) or iron oxide yellow (15mg capsule), iron oxide black, gelatin.

Zoton granules for suspension contain 30 mg of lansoprazole and the following inactive ingredients:

Magnesium carbonate, sucrose, starch-maize, hydroxypropylcellulose, methacrylic acid copolymer, talc, macrogol 8000, titanium dioxide, polysorbate 80, colloidal anhydrous silica, mannitol, docusate sodium, crospovidone, xanthan gum, strawberry flavour (J2161), citric acid monohydrate, iron oxide red, magnesium stearate.

PHARMACOLOGY

Actions

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was ≤30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	Final Visit[a] % (n/N)
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic

freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole (p≤0.001). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine (p <0.001 for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88 % with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * (p≤0.001) versus lansoprazole 15 mg and 30 mg; # (p≤0.001) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*(p≤0.001) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime
NT = Night-time
H = Heartburn
EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer. Patients whose gastric or duodenal ulcer 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.
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age.

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed, and the capsules should be swallowed whole and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.

- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an in vivo assay of chromosomal damage. In vitro assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in foetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be co-administered with atazanavir.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs is strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Zoton 15 mg or 30 mg capsules should be swallowed whole. Do not crush or chew (see PRECAUTIONS).

Zoton enteric-coated granules for oral suspension (30 mg) may be particularly useful for those patients who have difficulty swallowing, such as the elderly or patients with oesophageal stricture of dysphagia caused by severe oesophagitis.

Adults

Reflux oesophagitis: 30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer: 30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer: 30 mg lansoprazole once daily for 8 weeks.

Acid-related dyspepsia: Lansoprazole 15 mg or 30 mg once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of *H. pylori*: The following combinations have been shown to be effective when used for 7 days:

- Lansoprazole 30 mg twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

Instructions for patients who are unable to swallow capsules:

Patients requiring a 30 mg dose may be prescribed the sachets containing 30 mg granules for suspension. For other patients who have difficulty swallowing Zoton capsules, the capsule can be opened and administered as follows:

- Open the capsule.
- Sprinkle intact granules on one tablespoon of apple sauce, strained pears, cottage cheese or yoghurt.

- Swallow immediately.

The capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

- Open the capsule.
- Sprinkle intact granules into a small volume of apple juice, orange juice or tomato juice.
- Mix briefly and swallow immediately.
- To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

Use in other foods or liquids has not been studied clinically and is, therefore, not recommended.

Patient instructions for reconstituting 30 mg suspension from sachets:

- Add 30 mL of water to a glass.
- Empty the granules from a sachet into the glass.
- Stir well and drink immediately.

Nasogastric tube administration:

For patients who have a nasogastric tube in place, Zoton capsules can be administered as follows:

- Open the capsule.
- Mix intact granules into 40 mL of apple juice. DO NOT USE OTHER LIQUIDS.
- Inject through the nasogastric tube into the stomach.
- Flush with additional apple juice to clear the tube.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION AND STORAGE CONDITIONS

Zoton FasTabs 15 mg and 30 mg tablets

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with “15” or “30” debossed on one side of the tablet. Zoton FasTabs are supplied in blister packs of 7 or 28 tablets.

Zoton capsules* 15 mg

Hard gelatin yellow capsules with “Zoton” and “15 mg” markings.

Zoton capsules* 30 mg

Hard gelatin, lavender and amethyst coloured capsules with "Lederle" and "30 mg" markings.

Each capsule contains lansoprazole in enteric-coated granules.

Zoton capsules are available in a blister pack containing 30 capsules.

Zoton granules* for suspension 30 mg

Homogeneous fine pink granules for oral suspension, containing white to off-white pellets. When reconstituted in water, the granules give a pink suspension with a strawberry flavour.

Zoton granules for suspension 30 mg is available in laminated foil sachets in cartons of 28 sachets.

Zoton FasTabs, capsules* and granules* for suspension should be stored below 25ºC.

Once opened, Zoton granules* for suspension should be suspended in water and consumed immediately.

(*This presentation is not marketed.)

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – prescription only

TGA APPROVAL DATE: 7 January 2009

DATE OF MOST RECENT AMENDMENT: 16 March 2012

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Proprietor of the Trademark Zoton®

Zoton FasTabs®

Lansoprazole Tablets

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Zoton FasTabs. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. Your doctor has weighed the risks of you taking Zoton FasTabs against the benefits this medicine is expected to have.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may need to read it again.

What Zoton FasTabs is used for

Peptic Ulcers

Zoton FasTabs is used to treat peptic ulcers in adults. Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

Too much acid being made in the stomach can cause these ulcers. Zoton FasTabs is also used to help stop duodenal ulcers from coming back.

Reflux Oesophagitis

Zoton FasTabs is used to treat the symptoms of reflux oesophagitis or reflux disease in adults and in children from 6 to 17 years of age.

This can be caused by backflow (reflux) of food and acid from the stomach into the food pipe or gullet, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Heartburn and stomach pain associated with reflux or peptic ulcer

Zoton FasTabs is used for the short-term treatment of heartburn and peptic ulcer symptoms in adults.

Peptic Ulcers Associated with Helicobacter Pylori Infection

Most people who have a peptic ulcer also have bacteria called Helicobacter pylori in their stomach. Zoton FasTabs can be taken in conjunction with certain antibiotics to help eradicate Helicobacter pylori and let your peptic ulcer heal. However, it is possible that the antibiotics may not always get rid of Helicobacter pylori.

How Zoton FasTabs works

Zoton FasTabs contains lansoprazole, which is a type of medicine called a proton pump inhibitor (PPI). It works by decreasing the amount of acid the stomach makes, to give relief from the symptoms of excessive acid and allow healing to take place. This does not stop food being digested in the normal way.

Ask your doctor if you have any questions about why Zoton FasTabs has been prescribed for you.

Your doctor may prescribe this medicine for another reason.

There is no evidence that Zoton FasTabs is habit-forming. This medicine is available only with a doctor's prescription.

Before you take Zoton FasTabs

When you must not take it

1. **Do not take Zoton FasTabs if you have an allergy to:**

- Lansoprazole
- Any medicines containing a proton-pump inhibitor
- Any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction include rash, itching, or hives on the skin; shortness of breath, wheezing or difficulty breathing; and swelling of the face, lips, tongue or other parts of the body.

2. **Do not take Zoton FasTabs if you have severe liver disease.**
3. **Do not take Zoton FasTabs after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.**

   If it has expired or is damaged, return it to your pharmacist for disposal.
4. **Do not take Zoton FasTabs if you are already taking the medicine atazanavir.**

   Atazanavir is used to treat HIV infection. If it is taken at the same time as Zoton FasTabs, it won't be absorbed properly and will be less effective in treating HIV infection.

If you are not sure whether you should take this medicine, talk to your doctor.

Before you start to take it

You must tell your doctor if:

1. **You have any allergies to any other medicines, foods, dyes or preservatives.**
2. **You are pregnant or breast-feeding or intend to become pregnant or breast-feed.**

   Your doctor will discuss the possible risks and benefits of using Zoton FasTabs during pregnancy. It is not known if your baby can take in Zoton FasTabs from breast milk if you are breastfeeding. The use of Zoton FasTabs during breast-feeding should be avoided.
3. **You have any other medical conditions, including:**

- Liver or kidney problems.
- A tumour in the stomach region.

If you have not told your doctor about any of the above, tell them before you take Zoton FasTabs.

Taking other medicines

Tell your doctor if you are taking any other medicines, including medicines that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Zoton FasTabs. These medicines and their typical uses include:

- Theophylline used to treat asthma
- Oral contraceptives
- Warfarin used to prevent blood clots
- Carbamazepine and phenytoin used to treat seizures
- Ketoconazole used to treat fungal infections
- Digoxin used to treat heart complaints
- Sucralfate (used to treat gastric ulcers) and antacids (used to treat heartburn and indigestion).

  Zoton FasTabs should be taken at least one hour before taking sucralfate or an antacid.
- Iron preparations
- Ampicillin esters used in some antibiotics.
- Tacrolimus used in transplant patients to reduce organ rejection.
- Atazanavir used to treat HIV infection.

These medicines may be affected by Zoton FasTabs, or may affect how well it works. You may need different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

How to take Zoton FasTabs

Follow all directions given to you by your doctor or pharmacist carefully.

They may differ from the information contained in this leaflet.

If you do not understand the instructions on the box, ask your doctor or pharmacist for help.

When to take it

Take Zoton FasTabs in the morning before food.

Zoton FasTabs works best when taken on an empty stomach.

How much to take

Take one tablet each day, unless your doctor has told you otherwise.

Adults

The dose is usually 30 mg a day. The dose may vary from 15 mg to 30 mg a day depending on what the condition is and how long you need treatment.

Children (6 years or older)

The recommended dose depends on the weight of the child.

For children weighing 30 kg or less, the usual dose is 15 mg daily.

For children weighing over 30 kg, the usual dose is one 30 mg tablet daily.

How to take it

Swallow the tablet whole with a glass of water, or gently suck the tablet, then swallow the granules with your saliva.

If the tablet is chewed or crushed, it will not work properly.

How long to take it

Keep taking Zoton FasTabs as directed, unless your doctor gives you other instructions.

In most patients, Zoton FasTabs relieves symptoms rapidly and healing is usually complete within 4 weeks. However, you may find that the pain and discomfort caused by an ulcer or heartburn will go away well before you finish taking all your medicine.

Although Zoton FasTabs heals ulcers very successfully, the ulcer may come back at a later date. Your doctor may want you to keep taking Zoton FasTabs on a long-term basis to prevent the condition from coming back. However, Zoton FasTabs is recommended only for short-term use (8 to 12 weeks) in children.

Tell your doctor if your symptoms return.

You may need further treatment.

If you forget to take it

If it is almost time for the next dose, skip the missed dose and take the next dose when you are meant to. Otherwise, take it as soon as you remember, and then go back to your normal routine.

Do not take a double dose to make up for the dose you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (Tel 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Zoton FasTabs. Do this even if there are no signs of discomfort or poisoning.

While you are taking Zoton FasTabs

Things you must do

Take Zoton FasTabs exactly as your doctor has prescribed.

Tell your doctor if you become pregnant while you are taking Zoton FasTabs.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking Zoton FasTabs.

Things you must not do

Do not give your medicine to anyone else, even if they have the same condition as you.

Do not take Zoton FasTabs to treat any other complaints unless your doctor tells you to.

Do not stop taking your medicine or change the dosage without checking with your doctor.

If you stop taking it suddenly, your condition may worsen or you may have unwanted side effects.

Things to be careful of

Be careful driving or operating machinery until you know how Zoton FasTabs affects you.

Zoton FasTabs generally does not cause any problems with your ability to drive a car or operate machinery. However, as with many other medicines, Zoton FasTabs may cause dizziness in some people. Make sure you know how you react to Zoton FasTabs before you drive a car, operate machinery, or do anything else that could be dangerous if you are dizzy. If you drink alcohol, dizziness may be worse.

Things that may help your condition

Some self help measures suggested below may help your condition. Talk to your doctor or pharmacist about these measures and for more information.

- **Alcohol -**

  your doctor may advise you to limit your alcohol intake.

- **Aspirin and many other medicines used to treat arthritis, period pain or headaches -**

  these medicines may irritate the stomach and may make your condition worse. Your doctor or pharmacist may suggest other medicines you can take.

- **Caffeine -**

  your doctor may advise you to limit the number of drinks that contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate the stomach.

- **Eating habits -**

  eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times. Eat your meals well before bedtime.

- **Smoking -**

  your doctor may advise you to stop smoking or at least cut down.

- **Weight -**

  your doctor may suggest losing some weight to help your condition.

Side effects

Tell your doctor as soon as possible if you do not feel well while taking Zoton FasTabs.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Ask your doctor or pharmacist any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

Stomach or bowel problems such as:

- Vomiting or nausea
- Diarrhoea or constipation
- Stomach pain
- Indigestion
- Flatulence or wind.

If you suffer from severe persistent diarrhoea and/or vomiting when taking Zoton FasTabs, tell your doctor.

As natural acid in the stomach helps to kill bacteria, the lowering of acid by acid-reducing medicines such as Zoton FasTabs may cause some people to get certain stomach infections.

Difficulty thinking or working because of:

- Headache
- Dizziness
- Tiredness
- Joint or muscle aches or pains
- Generally feeling unwell
- Feeling confused, depressed or having hallucinations.

Changes to your appearance such as:

- Skin rashes
- Hives or itchy skin
- Hair thinning
- Increased sensitivity to sunlight
- Breast enlargement and impotence in men with long term use.

Signs of infection such as:

- Coughs, colds, sore throats or sinuses indicating an upper respiratory tract infection

- Frequent and painful passing of urine indicating a urinary tract infection
- Dry or sore mouth or throat.

Changes in your sight, hearing, taste or touch such as:

- Tingling or numbness of hands and feet
- Blurred vision
- Taste disturbances.

Tell your doctor immediately or go to Accident and Emergency at your nearest hospital if you notice any of the following:

- Red, itchy blistering spots
- Yellowing of the skin or eyes, especially if accompanied by fever, fatigue, loss of appetite, dark coloured urine or light coloured bowel movements
- Watery and severe diarrhoea
- Pain in the kidney region
- Swelling of the face, lips, tongue or throat, which may cause difficulty breathing
- Swelling of hands, ankles or feet
- Bruising or bleeding more easily than normal, bleeding under the skin or red or purple flat pinhead spots under the skin
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers.
- Cramping of the muscles in your hands or feet
- Irregular heartbeat
- Fits or seizures

These are serious to very serious side effects. You may need urgent medical attention. These side effects are rare.

Other side effects not listed above may occur in some patients. Tell your doctor if you notice anything making you feel unwell when taking, or soon after finishing taking, Zoton FasTabs.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- Pain or indigestion occurring during treatment with Zoton FasTabs
- You begin to vomit blood or food
- You pass black (blood-stained) motions.

Ask your doctor or pharmacist if you do not understand anything in this list.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

After taking Zoton FasTabs

Storage

Keep your tablets in their blister pack until it is time to take them.

If you take the tablets out of the blister pack they may not keep well.

Keep it in a cool dry place where the temperature stays below 25°C. Do not store it or any other medicines in a bathroom or near a sink. Do not leave it in the car or on windowsills.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop Zoton FasTabs or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product description

What it looks like

Zoton FasTabs 15 mg is available in a blister pack of 28 tablets.

Zoton FasTabs 30 mg is available in a blister pack of 7 or 28 tablets.

Zoton FasTabs 15mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" marked on one side.

Zoton FasTabs 30mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" marked on one side.

Ingredients

Each tablet contains either 15 mg or 30 mg of lansoprazole as the active ingredient and the following inactive ingredients:

Lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid - ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172), iron oxide red (E172), crospovidone, magnesium stearate, strawberry flavour and aspartame.

Zoton FasTabs do not contain gluten, tartrazine or any other azo dyes.

Australian Registration Number

Zoton FasTabs 15 mg tablets: AUST R 153575

Zoton FasTabs 30 mg tablets: AUST R 153701

Supplier

Pfizer Australia Pty Ltd

ABN 50 008 422 348

38-42 Wharf Road

WEST RYDE NSW 2114

Toll Free Number 1800 675 229

This leaflet was last revised in
December 2011.

PRODUCT INFORMATION

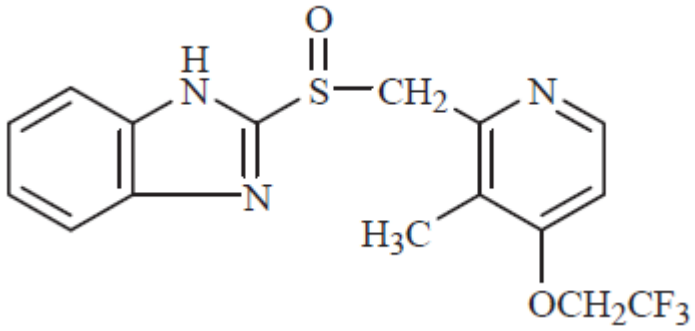
ZOTON® and ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8°C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole and the following inactive ingredients: Gastro-resistant microgranules: Lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients: crospovidone, magnesium stearate, strawberry flavour and aspartame.

Zoton capsules contain 15 mg or 30 mg of lansoprazole and the following inactive ingredients: Magnesium carbonate, sucrose, starch-maize, hydroxypropylcellulose, methacrylic acid copolymer, talc, macrogol 8000, titanium dioxide, polysorbate 80, colloidal anhydrous silica, erythrosine and indigo carmine (30mg capsule) or iron oxide yellow (15mg capsule), iron oxide black, gelatin.

Zoton granules for suspension contain 30 mg of lansoprazole and the following inactive ingredients:Magnesium carbonate, sucrose, starch-maize, hydroxypropylcellulose, methacrylic acid copolymer, talc, macrogol 8000, titanium dioxide, polysorbate 80, colloidal anhydrous silica, mannitol, docusate sodium, crospovidone, xanthan gum, strawberry flavour (J2161), citric acid monohydrate, iron oxide red, magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was ≤30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p\leq0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and

maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine (p <0.001 for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88 % with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * (p≤0.001) versus lansoprazole 15 mg and 30 mg; # (p≤0.001) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*(p≤0.001) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138

(44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer. Patients whose gastric or duodenal ulcer 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.
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed. The capsules should be swallowed whole and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection#

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A "no effect" dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in foetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline,

phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be co-administered with atazanavir.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs is strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Zoton 15 mg or 30 mg capsules should be swallowed whole. Do not crush or chew (see PRECAUTIONS).

Zoton enteric-coated granules for oral suspension (30 mg) may be particularly useful for those patients who have difficulty swallowing, such as the elderly or patients with oesophageal stricture of dysphagia caused by severe oesophagitis.

Adults

Reflux oesophagitis: 30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer: 30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer: 30 mg lansoprazole once daily for 8 weeks.

Acid-related dyspepsia: Lansoprazole 15 mg or 30 mg once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of *H. pylori*: The following combinations have been shown to be effective when used for 7 days:

- Lansoprazole 30 mg twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

Instructions for patients who are unable to swallow capsules

Patients requiring a 30 mg dose may be prescribed the sachets containing 30 mg granules for suspension. For other patients who have difficulty swallowing Zoton capsules, the capsule can be opened and administered as follows:

- Open the capsule.
- Sprinkle intact granules on one tablespoon of apple sauce, strained pears, cottage cheese or yoghurt.
- Swallow immediately.

The capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

- Open the capsule.
- Sprinkle intact granules into a small volume of apple juice, orange juice or tomato juice.
- Mix briefly and swallow immediately.
- To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

Use in other foods or liquids has not been studied clinically and is, therefore, not recommended.

Patient instructions for reconstituting 30 mg suspension from sachets

- Add 30 mL of water to a glass.
- Empty the granules from a sachet into the glass.
- Stir well and drink immediately.

Nasogastric tube administration

For patients who have a nasogastric tube in place, Zoton capsules can be administered as follows:

- Open the capsule.
- Mix intact granules into 40 mL of apple juice. DO NOT USE OTHER LIQUIDS.
- Inject through the nasogastric tube into the stomach.
- Flush with additional apple juice to clear the tube.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with “15” or “30” debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Zoton capsules* 15 mg: Hard gelatin yellow capsules with “Zoton” and “15 mg” markings.

Zoton capsules* 30 mg: Hard gelatin, lavender and amethyst coloured capsules with "Lederle" and "30 mg" markings.

Each capsule contains lansoprazole in enteric-coated granules. Zoton capsules are supplied in a blister pack containing 30 capsules.

Zoton granules* for suspension 30 mg: Homogeneous fine pink granules for oral suspension, containing white to off-white pellets. When reconstituted in water, the granules give a pink suspension with a strawberry flavour. Supplied in laminated foil sachets in cartons of 28 sachets.

Storage

Zoton FasTabs, capsules and granules should be stored below 25ºC.

Zoton granules for suspension should be stored below 25° C. Once opened the granules should be suspended in water and consumed immediately.

(* Presentation not available.)

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Presciption Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

Zoton capsules 15 mg: 10 July 1997.

Zoton capsules 30 mg: 20 September 1994.

Zoton granules for suspension 30 mg: 17 May 2001.

DATE OF MOST RECENT AMENDMENT

15 January 2014.

Please note change in Product Information.

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Zoton FasTabs®

Lansoprazole Tablets

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Zoton FasTabs. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. Your doctor has weighed the risks of you taking Zoton FasTabs against the benefits this medicine is expected to have.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may need to read it again.

What Zoton FasTabs is used for

Peptic Ulcers

Zoton FasTabs is used to treat peptic ulcers in adults. Depending on the position of the ulcer it is either a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

Too much acid being made in the stomach can cause these ulcers.

Zoton FasTabs is also used to help stop duodenal ulcers from coming back.

Reflux Oesophagitis

Zoton FasTabs is used to treat the symptoms of reflux oesophagitis or reflux disease in adults and in children from 6 to 17 years of age.

This can be caused by backflow (reflux) of food and acid from the stomach into the food pipe or gullet, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Heartburn and stomach pain associated with reflux or peptic ulcer.

Zoton FasTabs is used for the short-term treatment of heartburn and peptic ulcer symptoms in adults.

Peptic Ulcers Associated with Helicobacter Pylori Infection

Most people who have a peptic ulcer also have bacteria called Helicobacter pylori in their stomach. Zoton FasTabs can be taken in conjunction with certain antibiotics to help eradicate Helicobacter pylori and let your peptic ulcer heal. However, it is possible that the antibiotics may not always get rid of Helicobacter pylori.

How Zoton FasTabs works

Zoton FasTabs contains lansoprazole, which is a type of medicine called a proton pump inhibitor (PPI). It works by decreasing the amount of acid the stomach makes, to give relief from the symptoms of excessive acid and allow healing to take place. This does not stop food being digested in the normal way.

Ask your doctor if you have any questions about why Zoton FasTabs has been prescribed for you.

Your doctor may prescribe this medicine for another reason.

There is no evidence that Zoton FasTabs is habit-forming. This medicine is available only with a doctor's prescription.

Before you take Zoton FasTabs

When you must not take it

Do not take Zoton FasTabs if you have an allergy to:

- Lansoprazole
- Any medicines containing a proton-pump inhibitor
- Any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction include:

- rash, itching, or hives;
- shortness of breath, wheezing or difficulty in breathing;
- swelling of the face, lips, tongue or other parts of the body.

Do not take Zoton FasTabs if you have severe liver disease.

Do not take Zoton FasTabs if you are already taking the medicine atazanavir.

Atazanavir is used to treat HIV infection. If it is taken at the same time as Zoton FasTabs, it won't be absorbed properly and will be less effective in treating HIV infection.

Do not take Zoton FasTabs after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should take this medicine, talk to your doctor.

Before you start to take it

You must tell your doctor if:

You have any allergies to any other medicines, foods, dyes or preservatives.

You are pregnant, plan to become pregnant or are breast-feeding.

Your doctor will discuss the possible risks and benefits of taking Zoton FasTabs during pregnancy.

Taking Zoton FasTabs during breast-feeding should be avoided as it is not known if this medicine passes into your breast milk.

You have any other medical conditions, including:

- Liver or kidney problems
- Inflammation of the bowel
- A tumour in the stomach region.

You have problems with digestion, or have an intolerance to:

- Fructose
- Glucose
- Galactose
- Lactose
- Sucrose.

If you have not told your doctor about any of the above, tell him or her before you take Zoton FasTabs.

Taking other medicines

Tell your doctor if you are taking any other medicines, including medicines that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Zoton FasTabs. These medicines include:

- Theophylline used to treat asthma
- Oral contraceptives
- Warfarin used to prevent blood clots
- Carbamazepine and phenytoin used to treat seizures
- Ketoconazole used to treat fungal infections
- Digoxin used to treat heart complaints
- Sucralfate (used to treat gastric ulcers) and antacids (used to treat heartburn and indigestion).
- Zoton FasTabs should be taken at least one hour before taking sucralfate or an antacid.
- Iron preparations
- Ampicillin esters used in some antibiotics
- Tacrolimus used in transplant patients to reduce organ rejection
- Atazanavir used to treat HIV infection.

These medicines may be affected by Zoton FasTabs, or may affect how well it works. You may need different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

How to take Zoton FasTabs

Follow all directions given to you by your doctor or pharmacist carefully.

These may differ from the information contained in this leaflet.

If you do not understand the instructions on the box, ask your doctor or pharmacist for help.

When to take it

Take Zoton FasTabs in the morning before food.

Zoton FasTabs works best when taken on an empty stomach.

How much to take

Take one tablet each day, unless your doctor has told you otherwise.

Adults

The dose is usually 30 mg a day. The dose may vary from 15 mg to 30 mg a day depending on your condition.

Children (6 years or older)

The recommended dose depends on the weight of the child.

For children weighing 30 kg or less, the usual dose is 15 mg daily.

For children weighing over 30 kg, the usual dose is one 30 mg tablet daily.

How to take it

Swallow the tablet whole with a glass of water, or gently suck the tablet, then swallow the granules with your saliva.

Do not chew or crush the tablet as this affects how well Zoton FasTabs works.

How long to take it

Keep taking Zoton FasTabs as directed, unless your doctor gives you other instructions.

In most patients, Zoton FasTabs relieves symptoms rapidly and healing is usually complete within 4 weeks. In some patients a further 4 weeks of treatment may be needed for complete healing.

Your doctor may want you to keep taking Zoton FasTabs on a long-term basis to prevent the condition from coming back.

Zoton FasTabs is recommended only for short-term use (8 to 12 weeks) in children.

Tell your doctor if your symptoms return.

You may need further treatment.

If you forget to take it

If it is almost time for the next dose, skip the missed dose and take the next dose when you are meant to. Otherwise, take it as soon as you remember, and then go back to your normal routine.

Do not take a double dose to make up for the dose you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (Tel 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Zoton FasTabs. Do this even if there are no signs of discomfort or poisoning.

While you are taking Zoton FasTabs

Things you must do

Take Zoton FasTabs exactly as your doctor has prescribed.

Tell your doctor if you become pregnant while you are taking Zoton FasTabs.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking Zoton FasTabs.

Things you must not do

Do not give your medicine to anyone else, even if they have the same condition as you.

Do not take Zoton FasTabs to treat any other complaints unless your doctor tells you to.

Do not stop taking your medicine or change the dosage without checking with your doctor.

If you stop taking it suddenly, your condition may worsen or you may have unwanted side effects.

Things to be careful of

Be careful driving or operating machinery until you know how Zoton FasTabs affects you.

Zoton FasTabs generally does not cause any problems with your ability to drive a car or operate machinery. However, as with many other medicines, Zoton FasTabs may cause dizziness in some people. Make sure you know how you react to Zoton FasTabs before you drive a car, operate machinery, or do anything else that could be dangerous if you are dizzy. If you drink alcohol, dizziness may be worse.

Things that may help your condition

Some self help measures suggested below may help your condition. Talk to your doctor or pharmacist about these measures and for more information.

- **Alcohol**

  Your doctor may advise you to limit your alcohol intake.

- **Aspirin and many other medicines used to treat arthritis, period pain or headaches**

  These medicines may irritate the stomach and may make your condition worse. Your doctor or pharmacist may suggest other medicines you can take.

- **Caffeine**

  Your doctor may advise you to limit the number of drinks that contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate the stomach.

- **Eating habits**

  Eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times. Eat your meals well before bedtime.

- **Smoking**

  Your doctor may advise you to stop smoking or at least cut down.

- **Weight**

  Your doctor may suggest losing some weight to help your condition.

Side effects

Tell your doctor as soon as possible if you do not feel well while taking Zoton FasTabs.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the list of side effects.

You may not experience any of them.

Ask your doctor or pharmacist any questions you may have.

Tell your doctor if

Tell your doctor if you notice any of the following and they worry you:

Stomach or bowel problems such as:

- Vomiting or nausea
- Diarrhoea or constipation
- Stomach pain
- Indigestion
- Flatulence or wind.

If you suffer from severe persistent diarrhoea and/or vomiting when taking Zoton FasTabs, tell your doctor.

As natural acid in the stomach helps to kill bacteria, the lowering of acid by acid-reducing medicines such as Zoton FasTabs may cause some people to get certain stomach infections.

Difficulty thinking or working because of:

- Headache
- Dizziness
- Tiredness
- Joint or muscle aches or pains
- Generally feeling unwell
- Feeling confused, depressed or having hallucinations.

Changes to your appearance such as:

- Skin rashes
- Hives or itchy skin
- Hair thinning
- Breast enlargement and impotence in men with long term use.

Signs of infection such as:

- Coughs, colds, sore throats or sinuses indicating an upper respiratory tract infection
- Frequent and painful passing of urine indicating a urinary tract infection
- Dry or sore mouth or throat.

Changes in your sight, hearing, taste or touch such as:

- Tingling or numbness of hands and feet
- Blurred vision
- Increased sensitivity to sunlight
- Taste disturbances.

Tell your doctor immediately or go to Accident and Emergency at your nearest hospital if you notice any of the following:

- Red, itchy blistering spots
- Yellowing of the skin or eyes, especially if accompanied by fever, fatigue, loss of appetite, dark coloured urine or light coloured bowel movements
- Watery and severe diarrhoea
- Pain in the kidney region
- Swelling of the face, lips, tongue or throat, which may cause difficulty breathing
- Swelling of hands, ankles or feet
- Bruising or bleeding more easily than normal, bleeding under the skin or red or purple flat pinhead spots under the skin
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Cramping of the muscles in your hands or feet
- Irregular heartbeat
- Fits or seizures.

These are serious to very serious side effects. You may need urgent medical attention. These side effects are rare.

Other side effects not listed above may occur in some patients. Tell your doctor if you notice anything making you feel unwell when taking, or soon after finishing taking, Zoton FasTabs.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- Pain or indigestion occurring during treatment with Zoton FasTabs
- You begin to vomit blood or food
- You pass black (blood-stained) motions.

Ask your doctor or pharmacist if you do not understand anything in this list.

After taking Zoton FasTabs

Storage

Keep your tablets in their blister pack until it is time to take them.

If you take the tablets out of the blister pack they may not keep well.

Keep it in a cool dry place where the temperature stays below 25°C. Do not store it or any other medicines in a bathroom or near a sink. Do not leave it in the car or on windowsills.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop Zoton FasTabs or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product description

What it looks like

Zoton FasTabs 15 mg is available in a blister pack of 28 tablets.

Zoton FasTabs 30 mg is available in a blister pack of 7 or 28 tablets.

Zoton FasTabs 15 mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" marked on one side.

Zoton FasTabs 30 mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" marked on one side.

Ingredients

Zoton FasTabs contain either 15 mg or 30 mg of lansoprazole as the active ingredient.

Zoton FasTabs also contain the inactive ingredients:

- Lactose monohydrate
- Microcrystalline cellulose
- Heavy magnesium carbonate
- Low-substituted hydroxypropylcellulose
- Hydroxypropyl cellulose
- Hypromellose
- Titanium dioxide
- Talc
- Mannitol
- methacrylic acid - ethyl acrylate copolymer (1:1) 30 per cent
- Polyacrylate dispersion 30 per cent Macrogol 8000
- Citric acid anhydrous
- Glyceryl monostearate
- Polysorbate 80
- Triethyl citrate
- Iron oxide yellow (E172)
- Iron oxide red (E172)
- Crospovidone
- Magnesium stearate
- Strawberry flavour
- Aspartame.

Zoton FasTabs do not contain gluten, tartrazine or any other azo dyes.

Australian Registration Number

Zoton FasTabs 15 mg tablets: AUST R 153575.

Zoton FasTabs 30 mg tablets: AUST R 153701.

Supplier

Pfizer Australia Pty Ltd

ABN 50 008 422 348

38-42 Wharf Road

WEST RYDE NSW 2114.

Toll Free Number: 1800 675 229.

This leaflet was last revised in February 2014.

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PRODUCT INFORMATION

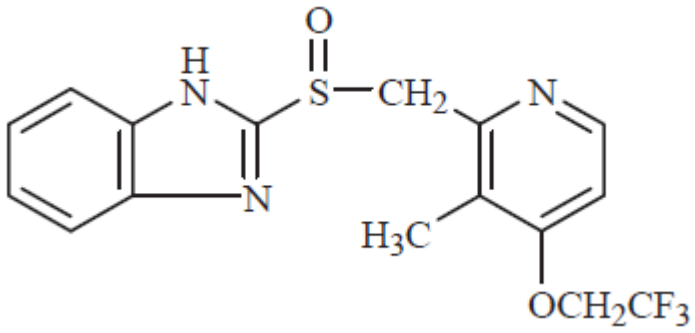
ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_3O_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole. The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and

gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was ≤30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	Final Visit[a] % (n/N)
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p\leq0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p <0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily,

88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * (p≤0.001) versus lansoprazole 15 mg and 30 mg; # (p≤0.001) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*(p≤0.001) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms

	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127	62/140	0.007	72/100	71/120	0.06

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No NT.EP	(61%) 79/115 (68%)	(45%) 59/120 (50%)	0.004	(72%) 74/91 (81%)	(60%) 67/104 (65%)	0.01

DT = Daytime
NT = Night-time
H = Heartburn
EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see DOSAGE AND ADMINISTRATION).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A "no effect" dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be co-administered with atazanavir.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer*

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Storage

Zoton FasTabs should be stored below 25 ºC.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

DATE OF MOST RECENT AMENDMENT

11 November 2014.

® Manufactured by and licensed from Takeda Chemical Industries, Osaka Japan.

Proprietor of the Trademark Zoton®

PRODUCT INFORMATION

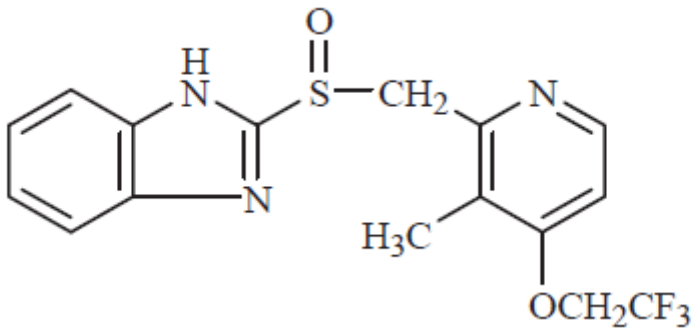
ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_3O_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole. The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent,

polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily

for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	Final Visit[a] % (n/N)
Erosive GORD healing rate	**100% (27/27)**
Improvement in overall GORD symptoms	**76% (47/62[b])**

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months

was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of “rescue” antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see DOSAGE AND ADMINISTRATION).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be co-administered with atazanavir.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

*Duodenal ulcer**

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

*Gastric ulcer**

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Storage

Zoton FasTabs should be stored below 25 ºC.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

DATE OF MOST RECENT AMENDMENT

02 June 2015.

® Manufactured by and licensed from Takeda Chemical Industries, Osaka Japan.
Proprietor of the Trademark Zoton®

PRODUCT INFORMATION

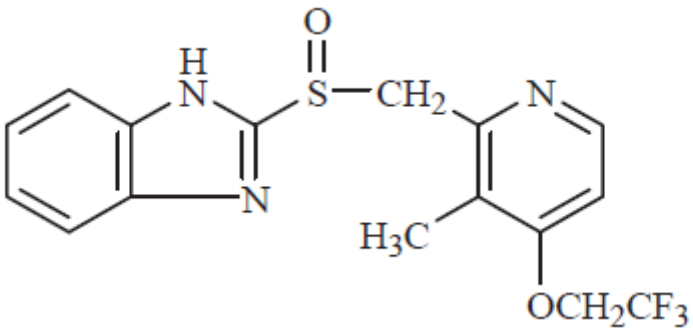
ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_3O_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole. The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent,

polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily

for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months

was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see DOSAGE AND ADMINISTRATION).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

*Duodenal ulcer**

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

*Gastric ulcer**

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Storage

Zoton FasTabs should be stored below 25 ºC.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

DATE OF MOST RECENT AMENDMENT

1 July 2015.

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Proprietor of the Trademark Zoton®

Zoton FasTabs®

Lansoprazole Tablets

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Zoton FasTabs. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. Your doctor has weighed the risks of you taking Zoton FasTabs against the benefits this medicine is expected to have.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may need to read it again.

What Zoton FasTabs is used for

Peptic Ulcers

Zoton FasTabs is used to treat peptic ulcers in adults. Depending on the position of the ulcer it is either a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

Too much acid being made in the stomach can cause these ulcers.

Zoton FasTabs is also used to help stop duodenal ulcers from coming back.

Reflux Oesophagitis

Zoton FasTabs is used to treat the symptoms of reflux oesophagitis or reflux disease in adults and in children from 6 to 17 years of age.

This can be caused by backflow (reflux) of food and acid from the stomach into the food pipe or gullet, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Heartburn and stomach pain associated with reflux or peptic ulcer.

Zoton FasTabs is used for the short-term treatment of heartburn and peptic ulcer symptoms in adults.

Peptic Ulcers Associated with Helicobacter Pylori Infection

Most people who have a peptic ulcer also have bacteria called Helicobacter pylori in their stomach. Zoton FasTabs can be taken in conjunction with certain antibiotics to help eradicate Helicobacter pylori and let your peptic ulcer heal. However, it is possible that the antibiotics may not always get rid of Helicobacter pylori.

How Zoton FasTabs works

Zoton FasTabs contains lansoprazole, which is a type of medicine called a proton pump inhibitor (PPI). It works by decreasing the amount of acid the stomach makes, to give relief from the symptoms of excessive acid and allow healing to take place. This does not stop food being digested in the normal way.

Ask your doctor if you have any questions about why Zoton FasTabs has been prescribed for you.

Your doctor may prescribe this medicine for another reason.

There is no evidence that Zoton FasTabs is habit-forming. This medicine is available only with a doctor's prescription.

Before you take Zoton FasTabs

When you must not take it

Do not take Zoton FasTabs if you have an allergy to:

- Lansoprazole
- Any medicines containing a proton-pump inhibitor
- Any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction include:

- rash, itching, or hives;
- shortness of breath, wheezing or difficulty in breathing;
- swelling of the face, lips, tongue or other parts of the body.

Do not take Zoton FasTabs if you have severe liver disease.

Do not take Zoton FasTabs if you are already taking the medicine atazanavir.

Atazanavir is used to treat HIV infection. If it is taken at the same time as Zoton FasTabs, it won't be absorbed properly and will be less effective in treating HIV infection.

Do not take Zoton FasTabs after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should take this medicine, talk to your doctor.

Before you start to take it

You must tell your doctor if:

You have any allergies to any other medicines, foods, dyes or preservatives.

You are pregnant, plan to become pregnant or are breast-feeding.

Your doctor will discuss the possible risks and benefits of taking Zoton FasTabs during pregnancy.

Taking Zoton FasTabs during breast-feeding should be avoided as it is not known if this medicine passes into your breast milk.

You have any other medical conditions, including:

- Liver or kidney problems
- Inflammation of the bowel
- A tumour in the stomach region.

You have problems with digestion, or have an intolerance to:

- Fructose
- Glucose
- Galactose
- Lactose
- Sucrose.

If you have not told your doctor about any of the above, tell him or her before you take Zoton FasTabs.

Taking other medicines

Tell your doctor if you are taking any other medicines, including medicines that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Zoton FasTabs. These medicines include:

- Theophylline used to treat asthma
- Oral contraceptives
- Warfarin used to prevent blood clots
- Carbamazepine and phenytoin used to treat seizures
- Ketoconazole used to treat fungal infections
- Digoxin used to treat heart complaints
- Sucralfate (used to treat gastric ulcers) and antacids (used to treat heartburn and indigestion)

Zoton FasTabs should be taken at least one hour before taking sucralfate or an antacid.

- Iron preparations
- Ampicillin esters used in some antibiotics
- Tacrolimus used in transplant patients to reduce organ rejection
- Atazanavir or other medicines used to treat HIV infection.

These medicines may be affected by Zoton FasTabs, or may affect how well it works. You may need different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

How to take Zoton FasTabs

Follow all directions given to you by your doctor or pharmacist carefully.

These may differ from the information contained in this leaflet.

If you do not understand the instructions on the box, ask your doctor or pharmacist for help.

When to take it

Take Zoton FasTabs in the morning before food.

Zoton FasTabs works best when taken on an empty stomach.

How much to take

Take one tablet each day, unless your doctor has told you otherwise.

Adults

The dose is usually 30 mg a day. The dose may vary from 15 mg to 30 mg a day depending on your condition.

Children (6 years or older)

The recommended dose depends on the weight of the child.

For children weighing 30 kg or less, the usual dose is 15 mg daily.

For children weighing over 30 kg, the usual dose is one 30 mg tablet daily.

How to take it

Swallow the tablet whole with a glass of water, or gently suck the tablet, then swallow the granules with your saliva.

Do not chew or crush the tablet as this affects how well Zoton FasTabs works.

How long to take it

Keep taking Zoton FasTabs as directed, unless your doctor gives you other instructions.

In most patients, Zoton FasTabs relieves symptoms rapidly and healing is usually complete within 4 weeks. In some patients a further 4 weeks of treatment may be needed for complete healing.

Your doctor may want you to keep taking Zoton FasTabs on a long-term basis to prevent the condition from coming back.

Zoton FasTabs is recommended only for short-term use (8 to 12 weeks) in children.

Tell your doctor if your symptoms return.

You may need further treatment.

If you forget to take it

If it is almost time for the next dose, skip the missed dose and take the next dose when you are meant to. Otherwise, take it as soon as you remember, and then go back to your normal routine.

Do not take a double dose to make up for the dose you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (Tel 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Zoton FasTabs. Do this even if there are no signs of discomfort or poisoning.

While you are taking Zoton FasTabs

Things you must do

Take Zoton FasTabs exactly as your doctor has prescribed.

Tell your doctor if you become pregnant while you are taking Zoton FasTabs.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking Zoton FasTabs.

Things you must not do

Do not give your medicine to anyone else, even if they have the same condition as you.

Do not take Zoton FasTabs to treat any other complaints unless your doctor tells you to.

Do not stop taking your medicine or change the dosage without checking with your doctor.

If you stop taking it suddenly, your condition may worsen or you may have unwanted side effects.

Things to be careful of

Be careful driving or operating machinery until you know how Zoton FasTabs affects you.

Zoton FasTabs generally does not cause any problems with your ability to drive a car or operate machinery. However, as with many other medicines, Zoton FasTabs may cause dizziness in some people. Make sure you know how you react to Zoton FasTabs before you drive a car, operate machinery, or do anything else that could be dangerous if you are dizzy. If you drink alcohol, dizziness may be worse.

Things that may help your condition

Some self-help measures suggested below may help your condition. Talk to your doctor or pharmacist about these measures and for more information.

- **Alcohol**

  Your doctor may advise you to limit your alcohol intake.

- **Aspirin and many other medicines used to treat arthritis, period pain or headaches**

  These medicines may irritate the stomach and may make your condition worse. Your doctor or pharmacist may suggest other medicines you can take.

- **Caffeine**

  Your doctor may advise you to limit the number of drinks that contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate the stomach.

- **Eating habits**

  Eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times. Eat your meals well before bedtime.

- **Smoking**

  Your doctor may advise you to stop smoking or at least cut down.

- **Weight**

  Your doctor may suggest losing some weight to help your condition.

Side effects

Tell your doctor as soon as possible if you do not feel well while taking Zoton FasTabs.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the list of side effects.

You may not experience any of them.

Ask your doctor or pharmacist any questions you may have.

Tell your doctor if...

Tell your doctor if you notice any of the following and they worry you:

Stomach or bowel problems such as:

- Vomiting or nausea
- Diarrhoea or constipation
- Stomach pain
- Indigestion
- Flatulence or wind.

If you suffer from severe persistent diarrhoea and/or vomiting when taking Zoton FasTabs, tell your doctor.

As natural acid in the stomach helps to kill bacteria, the lowering of acid by acid-reducing medicines such as Zoton FasTabs may cause some people to get certain stomach infections.

Difficulty thinking or working because of:

- Headache
- Dizziness
- Tiredness
- Joint or muscle aches or pains
- Generally feeling unwell
- Feeling confused, depressed or having hallucinations.

Changes to your appearance such as:

- Skin rashes
- Hives or itchy skin
- Hair thinning
- Breast enlargement and impotence in men with long term use.

Signs of infection such as:

- Coughs, colds, sore throats or sinuses indicating an upper respiratory tract infection
- Frequent and painful passing of urine indicating a urinary tract infection
- Dry or sore mouth or throat.

Changes in your sight, hearing, taste or touch such as:

- Tingling or numbness of hands and feet
- Blurred vision
- Increased sensitivity to sunlight
- Taste disturbances.

Go to hospital if...

Tell your doctor immediately or go to Accident and Emergency at your nearest hospital if you notice any of the following:

- Red, itchy blistering spots
- Yellowing of the skin or eyes, especially if accompanied by fever, fatigue, loss of appetite, dark coloured urine or light coloured bowel movements
- Watery and severe diarrhoea
- Pain in the kidney region
- Swelling of the face, lips, tongue or throat, which may cause difficulty breathing
- Swelling of hands, ankles or feet
- Bruising or bleeding more easily than normal, bleeding under the skin or red or purple flat pinhead spots under the skin
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Cramping of the muscles in your hands or feet
- Irregular heartbeat
- Fits or seizures.

These are serious to very serious side effects. You may need urgent medical attention. These side effects are rare.

Tell your doctor if you notice anything making you feel unwell when taking, or soon after finishing taking, Zoton FasTabs.

Other side effects not listed above may occur in some patients.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- Pain or indigestion occurring during treatment with Zoton FasTabs
- You begin to vomit blood or food
- You pass black (blood-stained) motions.

Ask your doctor or pharmacist if you do not understand anything in this list.

After taking Zoton FasTabs

Storage

Keep your tablets in their blister pack until it is time to take them.

If you take the tablets out of the blister pack they may not keep well.

Keep it in a cool dry place where the temperature stays below 25°C. Do not store it or any other medicines in a bathroom or near a sink. Do not leave it in the car or on windowsills.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop Zoton FasTabs or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product description

What it looks like

Zoton FasTabs 15 mg is available in a blister pack of 28 tablets.

Zoton FasTabs 30 mg is available in a blister pack of 7 or 28 tablets.

Zoton FasTabs 15 mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" marked on one side.

Zoton FasTabs 30 mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" marked on one side.

Ingredients

Zoton FasTabs contain either 15 mg or 30 mg of lansoprazole as the active ingredient.

Zoton FasTabs also contain the inactive ingredients:

- Lactose monohydrate
- Microcrystalline cellulose
- Heavy magnesium carbonate
- Low-substituted hydroxypropylcellulose
- Hydroxypropyl cellulose
- Hypromellose
- Titanium dioxide
- Talc
- Mannitol
- methacrylic acid - ethyl acrylate copolymer (1:1) 30 per cent
- Polyacrylate dispersion 30 per cent Macrogol 8000
- Citric acid anhydrous
- Glyceryl monostearate
- Polysorbate 80
- Triethyl citrate
- Iron oxide yellow (E172)
- Iron oxide red (E172)
- Crospovidone
- Magnesium stearate
- Strawberry flavour
- Aspartame.

Zoton FasTabs do not contain gluten, tartrazine or any other azo dyes.

Australian Registration Number

Zoton FasTabs 15 mg tablets: AUST R 153575.

Zoton FasTabs 30 mg tablets: AUST R 153701.

Supplier

Pfizer Australia Pty Ltd

ABN 50 008 422 348

38-42 Wharf Road

WEST RYDE NSW 2114.

Toll Free Number: 1800 675 229.

This leaflet was last revised in July 2015.

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PRODUCT INFORMATION

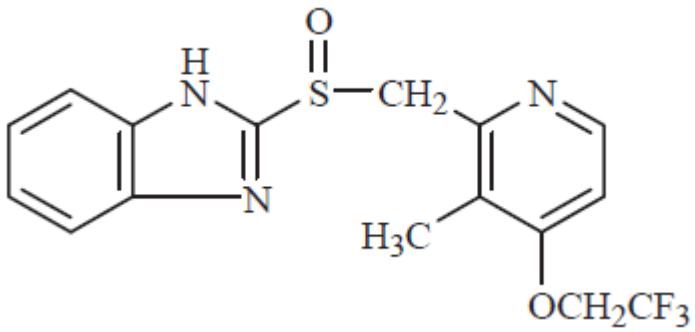
ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole. The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent,

polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily

for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months

was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see DOSAGE AND ADMINISTRATION).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer[*]

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer[*]

30 mg lansoprazole once daily for 8 weeks.

[*]Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	**Recommended Dose**
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

Contact the Poisons Information Centre on 131126 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Storage

Zoton FasTabs should be stored below 25 ºC.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

DATE OF MOST RECENT AMENDMENT

11 August 2015.

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Proprietor of the Trademark Zoton®

PRODUCT INFORMATION

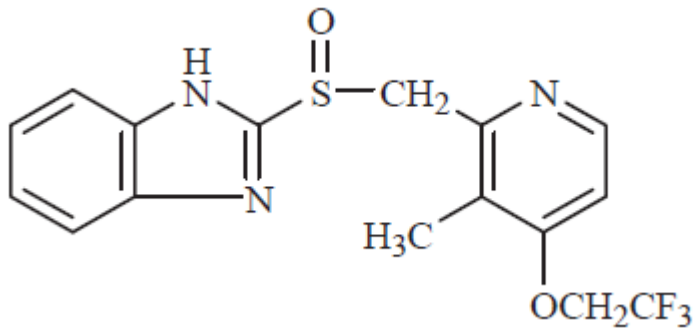
ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole. The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent,

polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily

for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months

was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see DOSAGE AND ADMINISTRATION).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study,

mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or

bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

Hypomagnesaemia has been reported rarely.

Fracture of the hip, wrist or spine has been reported.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer[*]

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	**Recommended Dose**
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

Contact the Poisons Information Centre on 131126 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Storage

Zoton FasTabs should be stored below 25 ºC.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

DATE OF MOST RECENT AMENDMENT

19 May 2016.

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Proprietor of the Trademark Zoton®

PRODUCT INFORMATION

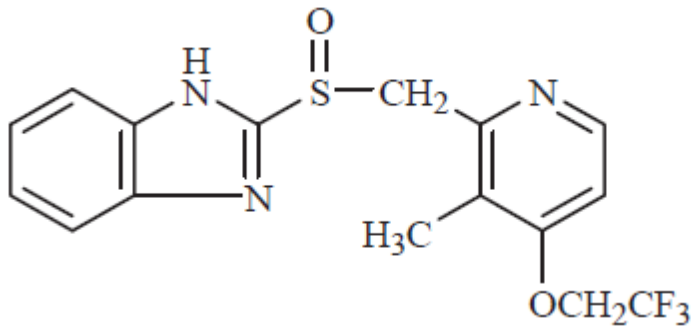
ZOTON® FasTabs

(lansoprazole)

NAME OF THE MEDICINE

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



CAS Registry Number: CAS No. 103577-45-3.

Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

DESCRIPTION

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole. The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, magnesium carbonate hydrate, low-substituted hyprolose, hyprolose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol

8000, citric acid, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172). Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Pharmacodynamics

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole

pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months

was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see DOSAGE AND ADMINISTRATION).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

PRECAUTIONS

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. Consider dose adjustment in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year

carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

There are insufficient data to recommend the administration of lansoprazole during pregnancy. Lansoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

INTERACTIONS WITH OTHER MEDICINES

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 would likely decrease the systemic exposure to lansoprazole. The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient.

Nervous system disorders

Headache, dizziness.

Rarely, paraesthesia and taste disturbances.

Psychiatric disorders

Depression, confusion and hallucinations.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

Infections and infestations

Upper respiratory tract infections, urinary tract infections.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Hepatobiliary disorders

Abnormal liver function test values, elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (γ-GTP).

Rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Skin and subcutaneous tissue disorders

Skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Immune system disorders

Angioedema, wheezing, and very rarely, anaphylactic reaction.

Renal and urinary disorders

Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Metabolism and nutrition disorders

Hypomagnesaemia has been reported rarely.

There have been isolated reports of hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Blood and lymphatic system disorders

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial pneumonia, but a definitive relationship to lansoprazole therapy has not been established.

Reproductive system and breast disorders

Gynaecomastia and erectile dysfunction have been reported rarely.

Injury, poisoning and procedural complications

Fracture of the hip, wrist or spine has been reported.

General disorders and administration site conditions

Fatigue, malaise, peripheral oedema.

DOSAGE AND ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer*

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	**Recommended Dose**
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

Contact the Poisons Information Centre on 131126 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Zoton FasTabs 15 mg and 30 mg tablets: White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Supplied in blister packs of 7 or 28 tablets.

Storage

Zoton FasTabs should be stored below 25 ºC.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine, S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

DATE OF MOST RECENT AMENDMENT

30 January 2017.

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Proprietor of the Trademark Zoton®

AUSTRALIAN PRODUCT INFORMATION - ZOTON® FasTabs (lansoprazole)

1. NAME OF THE MEDICINE

Zoton® FasTabs 15 mg and 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole.

Excipients with known effect

- Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with “15” or “30” debossed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see section 4.2).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see section 5.1, **Clinical Trials**).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see section 4.4). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer*

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Paediatric patients 6 to 11 years of age

In clinical studies, lansoprazole was not administered beyond 12 weeks in 6 to 11 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below (see Section 5.3 for nonclinical data).

Therapeutic indications	**Classification**	**Posology**
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 15 mg once daily for up to 12 weeks for children weighing ≤ 30 kg or 30 mg once daily for up to 12 weeks for children weighing > 30 kg.
Symptomatic Gastroesophageal reflux disease (s-GERD)		

Paediatric patients 12 to 17 years of age

In clinical studies, lansoprazole was not administered beyond 8 weeks in 12 to 17 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below.

Therapeutic indications	**Classification**	**Posology**
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 30 mg once daily for up to 8 weeks for erosive esophagitis
Symptomatic Gastroesophageal reflux disease (s-GERD)		The recommended dose is 1 mg once daily for up to 8 weeks for non-erosive GERD.

4.3 CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. Consider dose adjustment in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). 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 healthcare professional should consider stopping the product.

Use in the elderly

Dosage adjustment is not required in the elderly.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 would likely decrease the systemic exposure to lansoprazole. The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir and nelfinavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See section 5.3.

Use in pregnancy:

Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

There are insufficient data to recommend the administration of lansoprazole during pregnancy. Lansoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Zoton is well-tolerated, with adverse events generally being mild and transient.

Nervous system disorders

Headache, dizziness.

Rarely, paraesthesia and taste disturbances.

Psychiatric disorders

Depression, confusion and hallucinations.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence, and dry or sore mouth or throat.

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

Infections and infestations

Upper respiratory tract infections, urinary tract infections.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Hepatobiliary disorders

Abnormal liver function test values, elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (γ-GTP).

Rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Skin and subcutaneous tissue disorders

Skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Immune system disorders

Angioedema, wheezing, and very rarely, anaphylactic reaction.

Renal and urinary disorders

Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Metabolism and nutrition disorders

Hypomagnesaemia has been reported rarely.

There have been isolated reports of hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Blood and lymphatic system disorders

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial pneumonia, but a definitive relationship to lansoprazole therapy has not been established.

Reproductive system and breast disorders

Gynaecomastia and erectile dysfunction have been reported rarely.

Injury, poisoning and procedural complications

Fracture of the hip, wrist or spine has been reported.

General disorders and administration site conditions

Fatigue, malaise, peripheral oedema.

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 any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Clinical trials

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included

clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p\leq0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p <0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of “rescue” antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

5.2 PHARMACOKINETIC PROPERTIES

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid

inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study,

mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Juvenile Animal Studies

In an 8-week juvenile rat study, changes in male reproductive tissue (testes and epididymis) and heart (cardiac valve thickening) occurred at approximately 6-fold and 11-fold the expected human exposure, respectively, based on AUC (75-fold and 150-fold the expected human exposure based on body surface area). The findings reversed or trended towards reversibility after a 4-week drug-free recovery period.

The relevance of these findings to paediatric patients less than 12 years of age is unknown. The findings in this study are not relevant for patients 12 years of age and above

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, magnesium carbonate hydrate, low-substituted hyprolose, hyprolose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

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

Zoton FasTabs should be stored below 25 ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in blister packs of 7 or 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

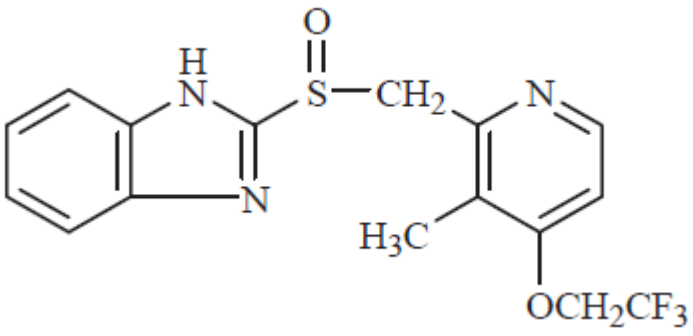
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

CAS number

CAS Registry Number: CAS No. 103577-45-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

10. DATE OF REVISION

27 June 2019

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Proprietor of the Trademark Zoton®

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Rebound acid hypersecretion adverse event
Section 8	Update to Sponsor address

Zoton FasTabs®

Lansoprazole Tablets

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Zoton FasTabs. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. Your doctor has weighed the risks of you taking Zoton FasTabs against the benefits this medicine is expected to have.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may need to read it again.

What Zoton FasTabs is used for

Peptic Ulcers

Zoton FasTabs is used to treat peptic ulcers in adults. Depending on the position of the ulcer it is either a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum, which is the tube leading out of the stomach.

Too much acid being made in the stomach can cause these ulcers.

Zoton FasTabs is also used to help stop duodenal ulcers from coming back.

Reflux Oesophagitis

Zoton FasTabs is used to treat the symptoms of reflux oesophagitis or reflux disease in adults and in children from 6 to 17 years of age.

This can be caused by backflow (reflux) of food and acid from the stomach into the food pipe or gullet, also known as the oesophagus.

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Heartburn and stomach pain associated with reflux or peptic ulcer.

Zoton FasTabs is used for the short-term treatment of heartburn and peptic ulcer symptoms in adults.

Peptic Ulcers Associated with Helicobacter Pylori Infection

Most people who have a peptic ulcer also have bacteria called Helicobacter pylori in their stomach. Zoton FasTabs can be taken in conjunction with certain antibiotics to help eradicate Helicobacter pylori and let your peptic ulcer heal. However, it is possible that the antibiotics may not always get rid of Helicobacter pylori.

How Zoton FasTabs works

Zoton FasTabs contains lansoprazole, which is a type of medicine called a proton pump inhibitor (PPI). It works by decreasing the amount of acid the stomach makes, to give relief from the symptoms of excessive acid and allow healing to take place. This does not stop food being digested in the normal way.

Ask your doctor if you have any questions about why Zoton FasTabs has been prescribed for you.

Your doctor may prescribe this medicine for another reason.

There is no evidence that Zoton FasTabs is habit-forming. This medicine is available only with a doctor's prescription.

Before you take Zoton FasTabs

When you must not take it

Do not take Zoton FasTabs if you have an allergy to:

- Lansoprazole
- Any medicines containing a proton-pump inhibitor
- Any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction include:

- rash, itching, or hives;
- shortness of breath, wheezing or difficulty in breathing;
- swelling of the face, lips, tongue or other parts of the body.

Do not take Zoton FasTabs if you have severe liver disease.

Do not take Zoton FasTabs if you are already taking the medicine atazanavir.

Atazanavir is used to treat HIV infection. If it is taken at the same time as Zoton FasTabs, it won't be absorbed properly and will be less effective in treating HIV infection.

Do not take Zoton FasTabs after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should take this medicine, talk to your doctor.

Before you start to take it

You must tell your doctor if:

You have any allergies to any other medicines, foods, dyes or preservatives.

You are pregnant, plan to become pregnant or are breast-feeding.

Your doctor will discuss the possible risks and benefits of taking Zoton FasTabs during pregnancy.

Taking Zoton FasTabs during breast-feeding should be avoided as it is not known if this medicine passes into your breast milk.

You have any other medical conditions, including:

- Liver or kidney problems
- Inflammation of the bowel
- A tumour in the stomach region.

You have problems with digestion, or have an intolerance to:

- Fructose
- Glucose
- Galactose
- Lactose
- Sucrose.

If you have not told your doctor about any of the above, tell him or her before you take Zoton FasTabs.

Taking other medicines

Tell your doctor if you are taking any other medicines, including medicines that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Zoton FasTabs. These medicines include:

- Theophylline used to treat asthma
- Oral contraceptives
- Warfarin used to prevent blood clots
- Carbamazepine and phenytoin used to treat seizures
- Ketoconazole used to treat fungal infections
- Digoxin used to treat heart complaints
- Sucralfate (used to treat gastric ulcers) and antacids (used to treat heartburn and indigestion)

Zoton FasTabs should be taken at least one hour before taking sucralfate or an antacid.

- Iron preparations
- Ampicillin esters used in some antibiotics
- Tacrolimus used in transplant patients to reduce organ rejection
- Atazanavir, nelfinavir or other medicines used to treat HIV infection
- Methotrexate used to treat some cancers.

These medicines may be affected by Zoton FasTabs, or may affect how well it works. You may need different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

How to take Zoton FasTabs

Follow all directions given to you by your doctor or pharmacist carefully.

These may differ from the information contained in this leaflet.

If you do not understand the instructions on the box, ask your doctor or pharmacist for help.

When to take it

Take Zoton FasTabs in the morning before food.

Zoton FasTabs works best when taken on an empty stomach.

How much to take

Take one tablet each day, unless your doctor has told you otherwise.

Adults

The dose is usually 30 mg a day. The dose may vary from 15 mg to 30 mg a day depending on your condition.

Children (6 years or older)

The recommended dose depends on the weight of the child.

For children weighing 30 kg or less, the usual dose is 15 mg daily.

For children weighing over 30 kg, the usual dose is one 30 mg tablet daily.

How to take it

Swallow the tablet whole with a glass of water, or gently suck the tablet, then swallow the granules with your saliva.

Do not chew or crush the tablet as this affects how well Zoton FasTabs works.

How long to take it

Keep taking Zoton FasTabs as directed, unless your doctor gives you other instructions.

In most patients, Zoton FasTabs relieves symptoms rapidly and healing is usually complete within 4 weeks. In some patients a further 4 weeks of treatment may be needed for complete healing.

In some cases, your doctor may decide that long-term treatment is needed.

Tell your doctor if any of your symptoms return after stopping long-term treatment.

Zoton FasTabs is recommended only for short-term use (8 to 12 weeks) in children.

For children aged 6-11 years, do not exceed 12 weeks of treatment with Zoton FasTabs.

For children aged 12-17 years, do not exceed 8 weeks of treatment with Zoton FasTabs.

Tell your doctor if your symptoms return.

You may need further treatment.

If you forget to take it

If it is almost time for the next dose, skip the missed dose and take the next dose when you are meant to. Otherwise, take it as soon as

you remember, and then go back to your normal routine.

Do not take a double dose to make up for the dose you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (Tel 13 11 26) for advice, or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Zoton FasTabs. Do this even if there are no signs of discomfort or poisoning.

While you are taking Zoton FasTabs

Things you must do

Take Zoton FasTabs exactly as your doctor has prescribed.

Tell your doctor if you become pregnant while you are taking Zoton FasTabs.

If you are about to start any new medicine, remind your doctor and pharmacist that you are taking Zoton FasTabs.

Things you must not do

Do not give your medicine to anyone else, even if they have the same condition as you.

Do not take Zoton FasTabs to treat any other complaints unless your doctor tells you to.

Do not stop taking your medicine or change the dosage without checking with your doctor.

If you stop taking it suddenly, your condition may worsen or you may have unwanted side effects.

Things to be careful of

Be careful driving or operating machinery until you know how Zoton FasTabs affects you.

Zoton FasTabs generally does not cause any problems with your ability to drive a car or operate machinery. However, as with many other medicines, Zoton FasTabs may cause dizziness in some people. Make sure you know how you react to Zoton FasTabs before you drive a car, operate machinery, or do anything else that could be dangerous if you are dizzy. If you drink alcohol, dizziness may be worse.

Things that may help your condition

Some self-help measures suggested below may help your condition. Talk to your doctor or pharmacist about these measures and for more information.

- **Alcohol**

  Your doctor may advise you to limit your alcohol intake.

- **Aspirin and many other medicines used to treat arthritis, period pain or headaches**

  These medicines may irritate the stomach and may make your condition worse. Your doctor or pharmacist may suggest other medicines you can take.

- **Caffeine**

  Your doctor may advise you to limit the number of drinks that contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate the stomach.

- **Eating habits**

  Eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times. Eat your meals well before bedtime.

- **Smoking**

  Your doctor may advise you to stop smoking or at least cut down.

- **Weight**

  Your doctor may suggest losing some weight to help your condition.

Side effects

Tell your doctor as soon as possible if you do not feel well while taking Zoton FasTabs.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the list of side effects.

You may not experience any of them.

Ask your doctor or pharmacist any questions you may have.

Tell your doctor if…

Tell your doctor if you notice any of the following and they worry you:

Stomach or bowel problems such as:

- Vomiting or nausea
- Diarrhoea or constipation
- Stomach pain
- Indigestion
- Flatulence or wind.

If you suffer from severe persistent diarrhoea and/or vomiting when taking Zoton FasTabs, tell your doctor.

As natural acid in the stomach helps to kill bacteria, the lowering of acid by acid-reducing medicines such as Zoton FasTabs may cause some people to get certain stomach infections.

Difficulty thinking or working because of:

- Headache
- Dizziness
- Tiredness
- Joint or muscle aches or pains
- Generally feeling unwell

- Feeling confused, depressed or having hallucinations.

Changes to your appearance such as:

- Skin rashes
- Hives or itchy skin
- Hair thinning
- Breast enlargement and impotence in men with long term use.

Signs of infection such as:

- Coughs, colds, sore throats or sinuses indicating an upper respiratory tract infection
- Frequent and painful passing of urine indicating a urinary tract infection
- Dry or sore mouth or throat.

Changes in your sight, hearing, taste or touch such as:

- Tingling or numbness of hands and feet
- Blurred vision
- Increased sensitivity to sunlight
- Taste disturbances.

Go to hospital if…

Tell your doctor immediately or go to Accident and Emergency at your nearest hospital if you notice any of the following:

- Red, itchy blistering spots, especially if it appears in areas of the skin that are exposed to the sun and is accompanied by joint pain
- Yellowing of the skin or eyes, especially if accompanied by fever, fatigue, loss of appetite, dark coloured urine or light coloured bowel movements
- Watery and severe diarrhoea
- Pain in the kidney region
- Swelling of the face, lips, tongue or throat, which may cause difficulty breathing
- Swelling of hands, ankles or feet
- Bruising or bleeding more easily than normal, bleeding under the skin or red or purple flat pinhead spots under the skin
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Cramping of the muscles in your hands or feet
- Irregular heartbeat
- Fits or seizures.

These are serious to very serious side effects. You may need urgent medical attention. These side effects are rare.

Tell your doctor if you notice anything making you feel unwell when taking, or soon after finishing taking, Zoton FasTabs.

Other side effects not listed above may occur in some patients.

Other problems are more likely to arise from the ulcer itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- Pain or indigestion occurring during treatment with Zoton FasTabs
- You begin to vomit blood or food
- You pass black (blood-stained) motions.

Ask your doctor or pharmacist if you do not understand anything in this list.

After taking Zoton FasTabs

Storage

Keep your tablets in their blister pack until it is time to take them.

If you take the tablets out of the blister pack they may not keep well.

Keep it in a cool dry place where the temperature stays below 25 °C. Do not store it or any other medicines in a bathroom or near a sink. Do not leave it in the car or on windowsills.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop Zoton FasTabs or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets that are left over.

Product description

What it looks like

Zoton FasTabs 15 mg is available in a blister pack of 28 tablets.

Zoton FasTabs 30 mg is available in a blister pack of 7 or 28 tablets.

Zoton FasTabs 15 mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" marked on one side.

Zoton FasTabs 30 mg tablets are white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" marked on one side.

Ingredients

Zoton FasTabs contain either 15 mg or 30 mg of lansoprazole as the active ingredient.

Zoton FasTabs also contain the inactive ingredients:

- Lactose monohydrate
- Microcrystalline cellulose
- Magnesium carbonate hydrate
- Low-substituted hyprolose
- Hyprolose
- Hypromellose
- Titanium dioxide
- Purified talc
- Mannitol
- Methacrylic acid - ethyl acrylate copolymer (1:1) 30 per cent

- Polyacrylate dispersion 30 per cent
- Macrogol 8000
- Citric acid
- Glyceryl monostearate
- Polysorbate 80
- Triethyl citrate
- Iron oxide yellow (E172)
- Iron oxide red (E172)
- Crospovidone
- Magnesium stearate
- Strawberry flavour
- Aspartame.

Zoton FasTabs do not contain gluten, tartrazine or any other azo dyes.

Australian Registration Number

Zoton FasTabs 15 mg tablets: AUST R 153575.

Zoton FasTabs 30 mg tablets: AUST R 153701.

Supplier

Pfizer Australia Pty Ltd

Sydney NSW

Toll Free Number: 1800 675 229.

This leaflet was prepared in June 2019

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AUSTRALIAN PRODUCT INFORMATION - ZOTON® FasTabs (lansoprazole)

1. NAME OF THE MEDICINE

Zoton® FasTabs 15 mg and 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole.

Excipients with known effect

- Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with “15” or “30” debossed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see section 4.2).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see section 5.1, **Clinical Trials**).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see section 4.4). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer*

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Paediatric patients 6 to 11 years of age

In clinical studies, lansoprazole was not administered beyond 12 weeks in 6 to 11 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below (see Section 5.3 for nonclinical data).

Therapeutic indications	**Classification**	**Posology**
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 15 mg once daily for up to 12 weeks for children weighing ≤ 30 kg or 30 mg once daily for up to 12 weeks for children weighing > 30 kg.
Symptomatic Gastroesophageal reflux disease (s-GERD)		

Paediatric patients 12 to 17 years of age

In clinical studies, lansoprazole was not administered beyond 8 weeks in 12 to 17 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below.

Therapeutic indications	**Classification**	**Posology**
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 30 mg once daily for up to 8 weeks for erosive esophagitis
Symptomatic Gastroesophageal reflux disease (s-GERD)		The recommended dose is 15 mg once daily for up to 8 weeks for non-erosive GERD.

4.3 CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. Consider dose adjustment in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). 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 healthcare professional should consider stopping the product.

Use in the elderly

Dosage adjustment is not required in the elderly.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 would likely decrease the systemic exposure to lansoprazole. The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir and nelfinavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See section 5.3.

Use in pregnancy:

Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

There are insufficient data to recommend the administration of lansoprazole during pregnancy. Lansoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Zoton is well-tolerated, with adverse events generally being mild and transient.

Nervous system disorders

Headache, dizziness.

Rarely, paraesthesia and taste disturbances.

Psychiatric disorders

Depression, confusion and hallucinations.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence, and dry or sore mouth or throat.

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

Infections and infestations

Upper respiratory tract infections, urinary tract infections.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Hepatobiliary disorders

Abnormal liver function test values, elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (γ-GTP).

Rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Skin and subcutaneous tissue disorders

Skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Immune system disorders

Angioedema, wheezing, and very rarely, anaphylactic reaction.

Renal and urinary disorders

Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Metabolism and nutrition disorders

Hypomagnesaemia has been reported rarely.

There have been isolated reports of hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Blood and lymphatic system disorders

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial pneumonia, but a definitive relationship to lansoprazole therapy has not been established.

Reproductive system and breast disorders

Gynaecomastia and erectile dysfunction have been reported rarely.

Injury, poisoning and procedural complications

Fracture of the hip, wrist or spine has been reported.

General disorders and administration site conditions

Fatigue, malaise, peripheral oedema.

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 any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Clinical trials

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included

clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p\leq0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p <0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of “rescue” antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

5.2 PHARMACOKINETIC PROPERTIES

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid

inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A “no effect” dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study,

mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Juvenile Animal Studies

In an 8-week juvenile rat study, changes in male reproductive tissue (testes and epididymis) and heart (cardiac valve thickening) occurred at approximately 6-fold and 11-fold the expected human exposure, respectively, based on AUC (75-fold and 150-fold the expected human exposure based on body surface area). The findings reversed or trended towards reversibility after a 4-week drug-free recovery period.

The relevance of these findings to paediatric patients less than 12 years of age is unknown. The findings in this study are not relevant for patients 12 years of age and above

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, magnesium carbonate hydrate, low-substituted hyprolose, hyprolose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

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

Zoton FasTabs should be stored below 25 ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in blister packs of 7 or 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

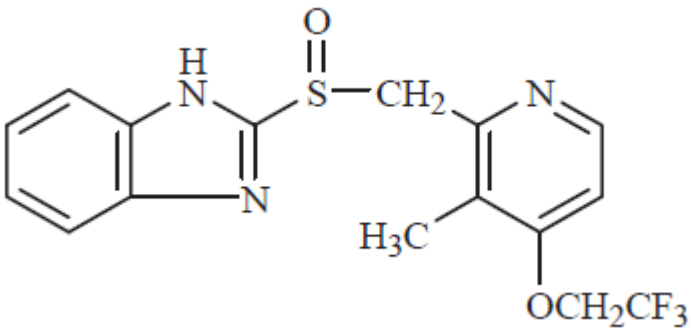
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

CAS number

CAS Registry Number: CAS No. 103577-45-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

10. DATE OF REVISION

14 August 2019

® Manufactured by and licensed from Takeda Chemical Industries, Osaka Japan.
Proprietor of the Trademark Zoton®

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Correction of dosing information for Paediatric patients 12 to 17 years of age

AUSTRALIAN PRODUCT INFORMATION – ZOTON FASTABS® (LANSOPRAZOLE)

1. NAME OF THE MEDICINE

Zoton® FasTabs 15 mg and 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole.

Excipient(s) with known effect

Zoton FasTabs contains lactose monohydrate and aspartame.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see Section 4.2 Dose and method of administration).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Section 5.1 Pharmacological properties, **Clinical Trials**).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

4.2 Dose and method of administration

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see Section 4.4 Special warnings and precautions for use). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer*

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Paediatric patients 6 to 11 years of age

In clinical studies, lansoprazole was not administered beyond 12 weeks in 6 to 11 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below (see Section 5.3 Preclinical safety data for nonclinical data).

Therapeutic indications	Classification	Posology
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 15 mg once daily for up to 12 weeks for children weighing ≤ 30 kg or 30 mg once daily for up to 12 weeks for children weighing > 30 kg.
Symptomatic Gastroesophageal reflux disease (s-GERD)		

Paediatric patients 12 to 17 years of age

In clinical studies, lansoprazole was not administered beyond 8 weeks in 12 to 17 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below.

Therapeutic indications	Classification	Posology
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 30 mg once daily for up to 8 weeks for erosive esophagitis
Symptomatic Gastroesophageal reflux disease (s-GERD)		The recommended dose is 15 mg once daily for up to 8 weeks for non-erosive GERD.

4.3 Contraindications

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

4.4 Special warnings and precautions for use

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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.

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). 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 healthcare professional should consider stopping the product.

Use in hepatic impairment Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. Consider dose adjustment in patients with severe hepatic impairment.

Use in renal impairment

There is no need to alter the dosage in adult patients with impaired renal function.

Use in the elderly

Dosage adjustment is not required in the elderly.

Paediatric use

See Section 4.2 Dose and method of administration – Paediatrics.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Effects on laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

4.5 Interactions with other medicines and other forms of interactions

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 would likely decrease the systemic exposure to lansoprazole. The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir and nelfinavir), due to

significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 5.3 Preclinical safety data.

Use in pregnancy – Pregnancy Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

There are insufficient data to recommend the administration of lansoprazole during pregnancy. Lansoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Zoton is well-tolerated, with adverse events generally being mild and transient.

Nervous system disorders

Headache, dizziness.

Rarely, paraesthesia and taste disturbances.

Psychiatric disorders

Depression, confusion and hallucinations.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence, and dry or sore mouth or throat.

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

Infections and infestations

Upper respiratory tract infections, urinary tract infections.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Hepatobiliary disorders

Abnormal liver function test values, elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (γ-GTP).

Rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Skin and subcutaneous tissue disorders

Skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Immune system disorders

Angioedema, wheezing, and very rarely, anaphylactic reaction.

Renal and urinary disorders

Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Metabolism and nutrition disorders

Hypomagnesaemia has been reported rarely.

There have been isolated reports of hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Blood and lymphatic system disorders

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial pneumonia, but a definitive relationship to lansoprazole therapy has not been established.

Reproductive system and breast disorders

Gynaecomastia and erectile dysfunction have been reported rarely.

Injury, poisoning and procedural complications

Fracture of the hip, wrist or spine has been reported.

General disorders and administration site conditions

Fatigue, malaise, 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 any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

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

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Clinical trials

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p\leq0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*(p≤0.001) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

5.2 Pharmacokinetic properties

Adults

Absorption

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Distribution

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Metabolism/Excretion

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

5.3 Preclinical safety data

Genotoxicity

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Carcinogenicity

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A "no effect" dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Juvenile Animal Studies

In an 8-week juvenile rat study, changes in male reproductive tissue (testes and epididymis) and heart (cardiac valve thickening) occurred at approximately 6-fold and 11-fold the expected human exposure, respectively, based on AUC (75-fold and 150-fold the expected human exposure based on body surface area). The findings reversed or trended towards reversibility after a 4-week drug-free recovery period. In a follow-up lansoprazole developmental sensitivity study, juvenile rats younger than postnatal Day 21 (age equivalent to approximately 2 years in humans) were more sensitive to the development of heart valve thickening, with valve thickening occurring at lower exposure (approximately 4-fold the expected human exposure based on AUC) in animals dosed starting at postnatal Day 14 (age equivalent to approximately 1 year in humans).

The relevance of these findings to paediatric patients less than 12 years of age is unknown. The findings in these studies are not relevant for patients 12 years of age and above.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, magnesium carbonate hydrate, low-substituted hyprolose, hyprolose, hypromellose, titanium dioxide, purified talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

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

Zoton FasTabs should be stored below 25 ºC.

6.5 Nature and contents of container

Supplied in blister packs of 7 or 28 tablets.

6.6 Special precautions for disposal

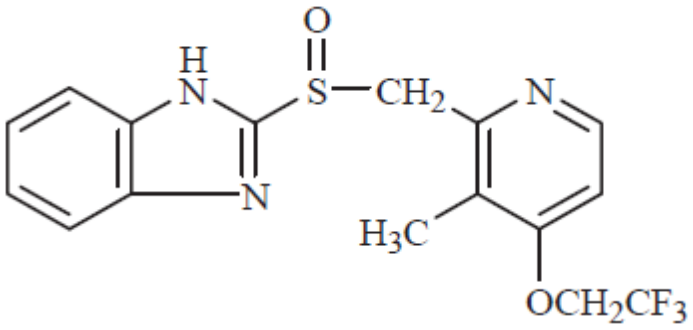
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

CAS number

CAS Registry Number: CAS No. 103577-45-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

10. DATE OF REVISION

3 December 2020

® Manufactured by and licensed from Takeda Chemical Industries, Osaka Japan.
Proprietor of the Trademark Zoton®

Summary Table of Changes

Section changed	Summary of new information
5.3	Addition of warning regarding the sensitivity of juvenile rats to heart valve thickening

AUSTRALIAN PRODUCT INFORMATION – ZOTON FASTABS® (LANSOPRAZOLE)

1. NAME OF THE MEDICINE

Zoton® FasTabs 15 mg and 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole.

Excipient(s) with known effect

Zoton FasTabs contains lactose monohydrate and aspartame.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see Section 4.2 Dose and method of administration).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Section 5.1 Pharmacological properties, **Clinical Trials**).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

4.2 Dose and method of administration

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see Section 4.4 Special warnings and precautions for use). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis

30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer*

30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer*

30 mg lansoprazole once daily for 8 weeks.

*Patients whose gastric or duodenal ulcer 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.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Paediatric patients 6 to 11 years of age

In clinical studies, lansoprazole was not administered beyond 12 weeks in 6 to 11 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below (see Section 5.3 Preclinical safety data for nonclinical data).

Therapeutic indications	Classification	Posology
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 15 mg once daily for up to 12 weeks for children weighing ≤ 30 kg or 30 mg once daily for up to 12 weeks for children weighing > 30 kg.
Symptomatic Gastroesophageal reflux disease (s-GERD)		

Paediatric patients 12 to 17 years of age

In clinical studies, lansoprazole was not administered beyond 8 weeks in 12 to 17 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below.

Therapeutic indications	Classification	Posology
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 30 mg once daily for up to 8 weeks for erosive esophagitis
Symptomatic Gastroesophageal reflux disease (s-GERD)		The recommended dose is 15 mg once daily for up to 8 weeks for non-erosive GERD.

4.3 Contraindications

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

4.4 Special warnings and precautions for use

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.
- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine; however, humans obtain their taurine requirements from the diet.

Acute Tubulointerstitial Nephritis (TIN)

Acute TIN has been observed in patients taking PPIs including lansoprazole. Acute TIN may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute TIN develops.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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).

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). 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 healthcare professional should consider stopping the product.

Use in hepatic impairment Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. Consider dose adjustment in patients with severe hepatic impairment.

Use in renal impairment

There is no need to alter the dosage in adult patients with impaired renal function.

Use in the elderly

Dosage adjustment is not required in the elderly.

Paediatric use

See Section 4.2 Dose and method of administration – Paediatrics.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Effects on laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

4.5 Interactions with other medicines and other forms of interactions

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 would likely decrease the systemic exposure to lansoprazole. The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Coadministration of PPIs 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 PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir and nelfinavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 5.3 Preclinical safety data.

Use in pregnancy – Pregnancy Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in fetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

There are insufficient data to recommend the administration of lansoprazole during pregnancy. Lansoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Zoton is well-tolerated, with adverse events generally being mild and transient.

Nervous system disorders

Headache and dizziness.

Rarely, paraesthesia and taste disturbances.

Psychiatric disorders

Depression, confusion and hallucinations.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence, and dry or sore mouth or throat.

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

Infections and infestations

Upper respiratory tract infections, urinary tract infections.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Hepatobiliary disorders

Abnormal liver function test values, elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (γ-GTP).

Rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Skin and subcutaneous tissue disorders

Skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Immune system disorders

Angioedema, wheezing, and very rarely, anaphylactic reaction.

Renal and urinary disorders

Cases of Tubulointerstitial Nephritis TIN have been reported which have sometimes resulted in renal failure.

Metabolism and nutrition disorders

Hypomagnesaemia has been reported rarely. Hypocalcaemia and hypokalaemia have been reported, which may be related to the occurrence of hypomagnesaemia (see section 4.4 Special Warnings and Precautions). There have been isolated reports of hyponatraemia.

Blood and lymphatic system disorders

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial pneumonia, but a definitive relationship to lansoprazole therapy has not been established.

Reproductive system and breast disorders

Gynaecomastia and erectile dysfunction have been reported rarely.

Injury, poisoning and procedural complications

Fracture of the hip, wrist or spine has been reported.

General disorders and administration site conditions

Fatigue, malaise, 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 any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

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

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Clinical trials

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms (p<0.001).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with

either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88% with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	**0-1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined

as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

5.2 Pharmacokinetic properties

Adults

Absorption

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

Distribution

Plasma protein binding is high (98%) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Metabolism/Excretion

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-labelled lansoprazole showed that up to 50% of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

5.3 Preclinical safety data

Genotoxicity

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Carcinogenicity

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A "no effect" dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Juvenile Animal Studies

In an 8-week juvenile rat study, changes in male reproductive tissue (testes and epididymis) and heart (cardiac valve thickening) occurred at approximately 6-fold and 11-fold the expected human exposure, respectively, based on AUC (75-fold and 150-fold the expected human exposure based on body surface area). The findings reversed or trended towards reversibility after a 4-week drug-free recovery period. In a follow-up lansoprazole developmental sensitivity study, juvenile rats younger than postnatal Day 21 (age equivalent to approximately 2 years in humans) were more sensitive to the development of heart valve thickening, with valve thickening occurring at lower exposure (approximately 4-fold the expected human exposure based on AUC) in animals dosed starting at postnatal Day 14 (age equivalent to approximately 1 year in humans).

The relevance of these findings to paediatric patients less than 12 years of age is unknown. The findings in these studies are not relevant for patients 12 years of age and above.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, magnesium carbonate hydrate, low-substituted hyprolose, hyprolose, hypromellose, titanium dioxide, purified talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

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

Zoton FasTabs should be stored below 25 ºC.

6.5 Nature and contents of container

Supplied in blister packs of 7 or 28 tablets.

6.6 Special precautions for disposal

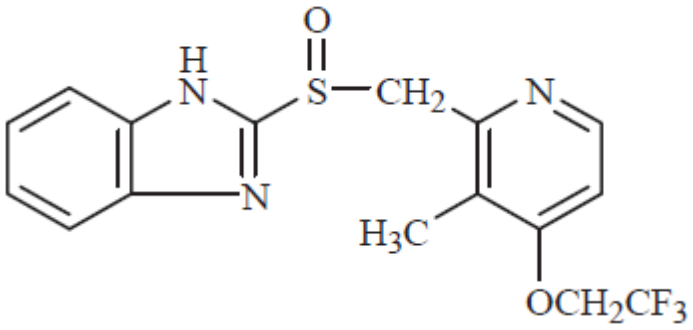
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 °C with decomposition and has a pKa of 8.8.

CAS number

CAS Registry Number: CAS No. 103577-45-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

10. DATE OF REVISION

15 April 2021

® Manufactured by and licensed from Takeda Chemical Industries, Osaka Japan.
Proprietor of the Trademark Zoton®

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of hypocalcaemia and hypokalaemia to existing hypomagnesaemia warning. References to Interstitial nephritis amended to Tubulointerstitial Nephritis (TIN).
4.8	Addition of hypokalaemia, hypocalcaemia and hyponatraemia adverse effects. Addition of DRESS adverse effect.

ZOTON® FasTabs 15 mg and 30 mg tablets

PRODUCT INFORMATION

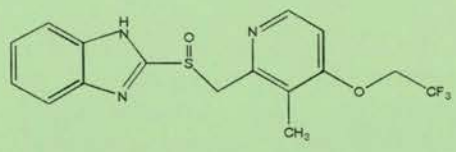
NAME OF THE MEDICINE

Lansoprazole

Chemical Name and Structure

2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

CAS No. 103577-45-3.



$C_{16}H_{14}F_3N_3O_2S$ MW 369.36

DESCRIPTION

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Inactive ingredients.

Gastro-resistant microgranules: Lactose monohydrate, microcrystalline cellulose, heavy magnesium carbonate, low-substituted hydroxypropylcellulose, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid anhydrous, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients: crospovidone, magnesium stearate, strawberry flavour and aspartame.

PHARMACOLOGY

Actions

Lansoprazole reduces gastric acid secretions by inhibiting the H+/K+-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80%. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90% inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

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When used in combination with the recommended antibiotics, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Pharmacokinetics

Adults

Lansoprazole is well absorbed and exhibits high bioavailability (80-90%) following an oral dose. The bioavailability has been shown to be affected by the presence of food; however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that a.m. dosing produced higher mean gastric pH values than p.m. dosing.

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CLINICAL TRIALS

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90%. The best eradication rates were obtained with regimens which included clarithromycin. Trials which used Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was ≤30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg,

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administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	Final Visit[a] % (n/N)
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p < 0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole, although this was not statistically significant.

A study in 266 patients, comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31% in the lansoprazole 15 mg group, 20% in the lansoprazole 30 mg group and 68% in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p < 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75% with lansoprazole 15 mg daily, 88 % with lansoprazole 30 mg daily and 89% with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below.

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	Placebo
1 (n=163)	37%	39%	-	-	92%*
2 (n=184)	13%	11%	-	-	-
3 (n=569)	31%	20%	68%*	-	-
4 (n=882)	25%#	12%	-	11%	-

- not included in the study; * ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg; # ($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months

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was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates

	Interval (months)					
Treatment	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20%	36%	52%	60%	60%	62%
Lansoprazole 15 mg	2%*	8%*	10%*	14%*	15%*	17%*

*($p \leq 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg, did not extend beyond 12 months.

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms

	Week 2			Week 4		
	Lansoprazole	Ranitidine	P value	Lansoprazole	Ranitidine	P value
No symptoms	95/171	56/171	0.001	95/137	63/145	0.001
	(55%)	(33%)		(69%)	(44%)	
No DT.H	91/138	68/139	0.006	89/111	66/120	0.001
	(66%)	(49%)		(80%)	(55%)	
No NT.H	89/128	64/124	0.005	86/103	68/106	0.003
	(69%)	(52%)		(83%)	(64%)	
No DT.EP	78/127	62/140	0.007	72/100	71/120	0.06
	(61%)	(45%)		(72%)	(60%)	
No NT.EP	79/115	59/120	0.004	74/91	67/104	0.01
	(68%)	(50%)		(81%)	(65%)	

DT =Daytime H =Heartburn
NT =Night-time EP =Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28

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% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	Symptom Free Patients n (%)		P value
		Lansoprazole	Omeprazole	
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group ($p=0.005$). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group ($p=1.0$). Healing was defined as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of $\leq 20\%$ during the last 5 days of treatment.

INDICATIONS

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer. Patients whose gastric or duodenal ulcer 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.
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Clinical Trials).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age.

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

CONTRAINDICATIONS

Hypersensitivity to lansoprazole, other proton pump inhibitors or any of the excipients in the tablets.
Severe hepatic impairment.

PRECAUTIONS

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As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

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 a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Carcinogenicity/mutagenicity, impairment of fertility

In a 2-year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A "no effect" dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2-year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78-week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an in vivo assay of chromosomal damage. In vitro assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long-term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies.

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- a slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.

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- single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.

- for antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.

- no evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine, however, humans obtain their taurine requirements from the diet.

Use in pregnancy: Category B3

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in foetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in the elderly

Dosage adjustment is not required in the elderly.

Impaired hepatic and renal function

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. There is no need to alter the dosage in adult patients with impaired renal function.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Interactions with other medicines

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system, e.g. theophylline, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs phenytoin (single IV doses only) and diazepam have been found.

The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of

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lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, ampicillin esters, iron salts, digoxin).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsoprtion or sucrase-isomaltase insufficiency should not take this medicine.

ADVERSE EFFECTS

Zoton is well-tolerated, with adverse events generally being mild and transient. The most commonly reported adverse events are headache, dizziness, fatigue and malaise.

Gastrointestinal effects include diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence and dry or sore mouth or throat.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Alterations in liver function test values and, rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Dermatological reactions include skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Other hypersensitivity reactions include angioedema, wheezing, and very rarely, anaphylaxis. Cases of interstitial nephritis have been reported which have sometimes resulted in renal failure.

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Other reactions include arthralgia, myalgia, depression, peripheral oedema, upper respiratory tract infections, urinary tract infections and, rarely, paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations.

There have been isolated reports of interstitial pneumonia and hyponatraemia, but a definitive relationship to lansoprazole therapy has not been established.

Gynaecomastia and impotence have been reported rarely.

DOSAGE AND ADMINISTRATION

For oral administration. Zoton FasTabs is strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see PRECAUTIONS). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

Reflux oesophagitis: 30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer: 30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer: 30 mg lansoprazole once daily for 8 weeks.

Acid-related dyspepsia: Lansoprazole 15 mg or 30 mg once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of *H. pylori*: The following combinations have been shown to be effective when used for 7 days:

- Lansoprazole 30 mg twice daily plus **two** of the following antibiotics: amoxycillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Short-term treatment (8-12 weeks). In patients aged 6-17 years with gastro-oesophageal reflux disease, including all grades of oesophagitis, the recommended initial dosage is:

Body weight	Recommended Dose
≤30 kg	15 mg lansoprazole once daily
>30 kg	30 mg lansoprazole once daily

After 2 weeks, an increase in dose up to 60 mg lansoprazole daily may be beneficial for patients who are not responding satisfactorily.

OVERDOSAGE

There is no information on the effect of acute overdosage. In a case of overdose, supportive and symptomatic therapy should be initiated. Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison syndrome with no serious adverse effects.

PRESENTATION

Zoton FasTabs 15 mg and 30 mg tablets

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet. Zoton FasTabs are supplied in blister packs of 7 or 28 tablets.

Storage

Store below 25°C.

Poison Schedule

S4, PRESCRIPTION ONLY MEDICINE.

NAME & ADDRESS OF SPONSOR

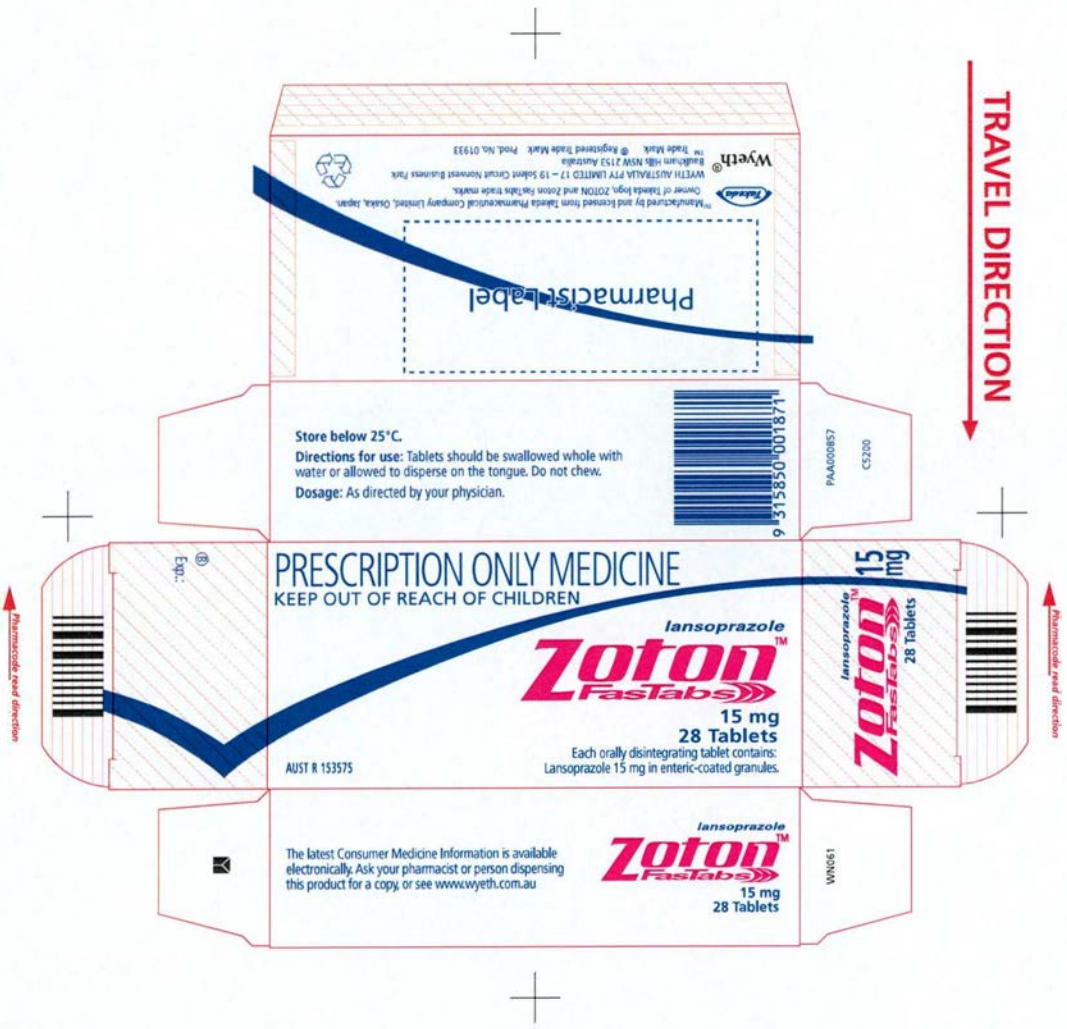
Wyeth Australia Pty Limited

ABN 16 000 296 211

17-19 Solent Circuit, Norwest Business Park, Baulkham Hills, NSW, 2153
☎(02) 8850 8200 or (02) 9761 8200

Manufactured by and licensed from Takeda Chemical Industries, Osaka Japan.
Proprietor of the Trade Mark Zoton ®

Date of TGA Approval:



Wyeth		
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	Wyeth Drawing No.	WN061
	Printer	MY Healthcare Waterford
	Date	16/04/04
	Version	01

Profile Keys:
Print Free (Excl. Tech. Info.) | Varnish Free | Copy/Text Free | Pharma Code

TEXT SIZE
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The SMALLEST text on this A/W is at:
6.0 pt

MRP Component Description: CTN ZOTON FASTAB 15mg 4X7 AUSTRALIA

Wyeth
European Packaging Services
Black | P273 | Magenta
Profile | Varnish

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Packaging Plant	Newbridge
Plant Ref No.	N/A
Profile No.	WN061
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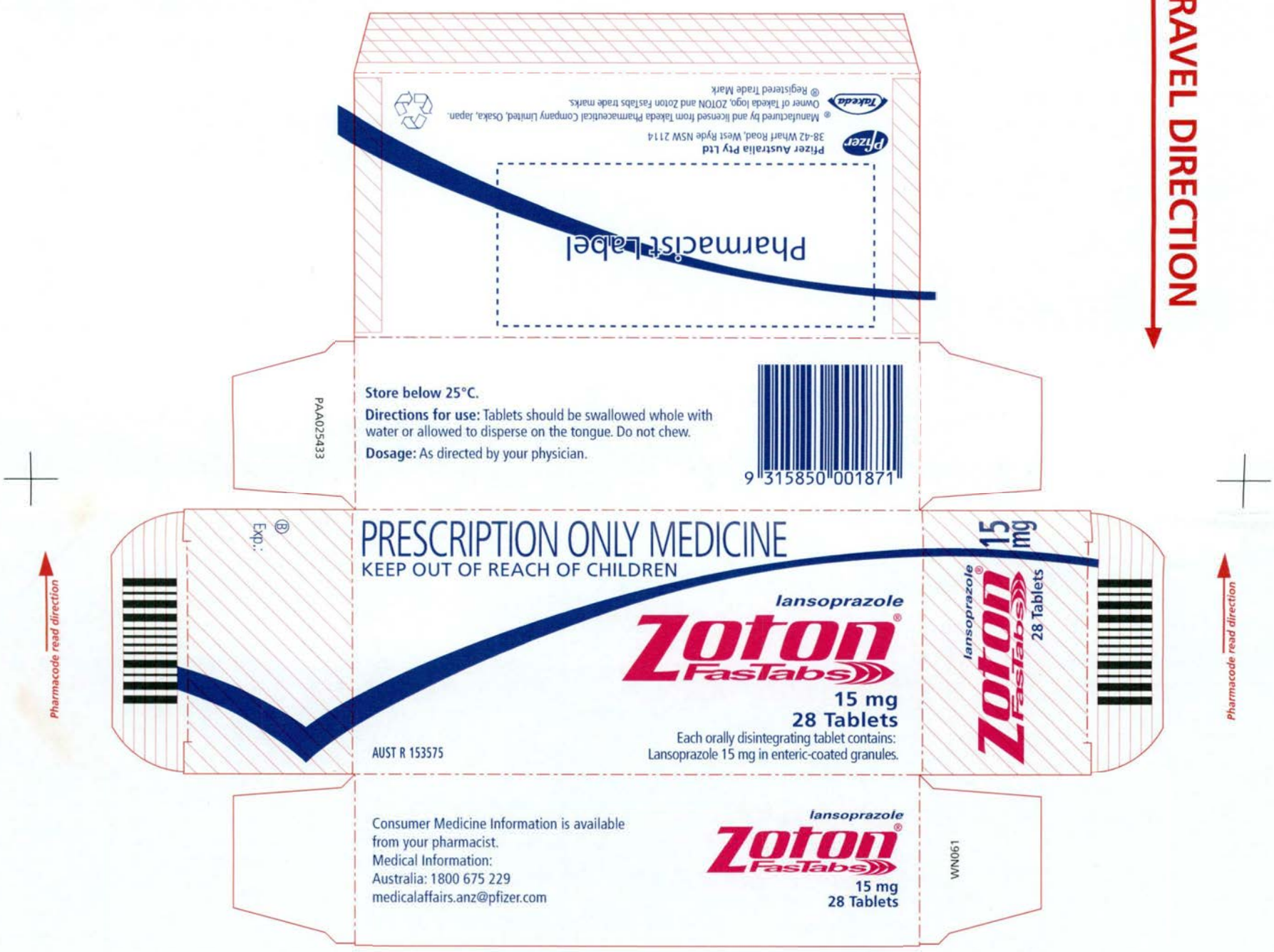
Pharma Code	6163
Barcode No.	9315850001871
Number of Colours	3 + Varnish
Pass No.	5
Printer	MY HEALTHCARE WATERFORD
Date last modified	20/01/09

Fonts: Frutiger, Fruitiger Condensed

Schawk Kingsway North, Team Valley Estate, Gateshead, Tyne and Wear NE11 0JH. Tel: +44 (0)191 491 7777

100% 95% 50% 5%

Pfizer Carton Label - 15mg
Actual size



Component	Carton
Pfizer Drawing No.	WN061
Date	22/09/10
Version	02.01

Profile Keys: Print Free (Excl. Tech. Info.) | Varnish Free | Copy/Text Free | Pharma Code | Braille Grid

Black | Magenta | P273 | Profile | Varnish

MRP Component Description:	CTN ZOTON FASTAB 15MG 4X7 AU
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Packaging Plant	NEWBRIDGE
Item Code	PAA025433
Pharma Code	7436
Barcode No.	9315850001871
Job No.	312182A02
Pass No.	2
Date last modified	02 Nov 11

100% | 95% | 50% | 5%

SCHAWK! Kingsway North, Newcastle Tyne & Wear NE11 0JH UK schawk.com T +44 (0) 191 491 7777 F +44 (0) 191 487 6673

TEXT SIZE
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The SMALLEST text on this A/W is at:
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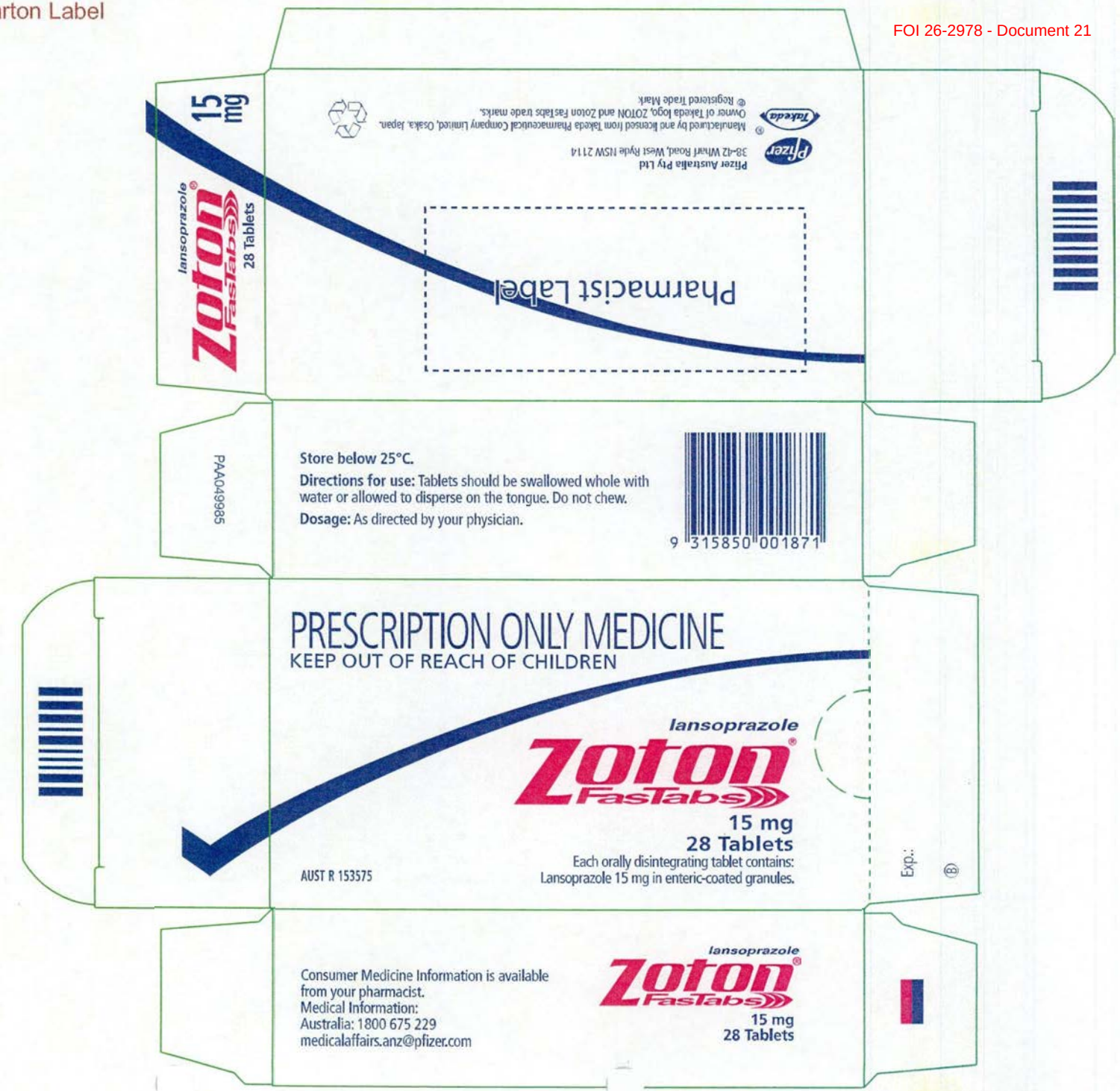
Proposed Zoton FasTabs 15 mg Carton Label
Scaled to 96% of Actual Size



Proposed Zoton FasTabs 15 mg Carton Label
Scaled to 96% of Actual Size