

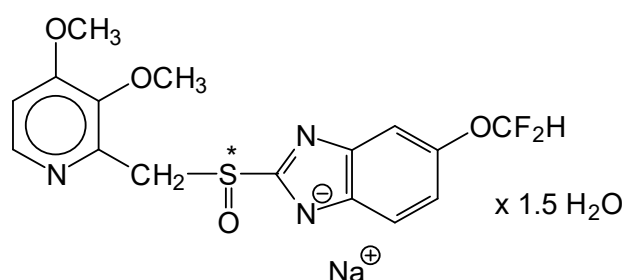
PRODUCT INFORMATION

SOMAC[®] pantoprazole (as pantoprazole sodium sesquihydrate) Tablets and Granules

NAME OF THE MEDICINE

Non-proprietary name: Pantoprazole (as pantoprazole sodium sesquihydrate)

The structure of pantoprazole sodium sesquihydrate is:



CAS Number: 138 786-67-1 (pantoprazole sodium)

The molecular weight of pantoprazole, sodium salt x 1.5 H₂O is 432.4.

DESCRIPTION

Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC 40 mg enteric coated tablets contain 45.1 mg pantoprazole sodium sesquihydrate.

SOMAC 20 mg enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate.

SOMAC 40 mg enteric coated granules contain 45.1 mg pantoprazole sodium sesquihydrate.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow (CI 77492), propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Brown S-1-16530 printing ink.

In addition to pantoprazole sodium, each unit dose sachet of granules also contains microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow (CI 77492), methacrylic acid copolymer, triethyl citrate, and purified talc.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H^+/K^+ -ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+ -ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($pH < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see Dosage & Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (δ 23%) with once daily dosing.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5 to 16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

Clinical Trials in Adults

Eradication of H pylori

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023/	Design	Therapy Scheme (mg per day)	Days of medication	n (MITT)	Indication (n)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8 %
		----- PAC 80/2000/1000	14/14/14	34		91.2 %
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0 %
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/ Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/ 7/ 7	30	DU (8), GU (3) HU (6), FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/ 7/ 7	121	DU (244)	73.6 %
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P			DU (62)	

Study BY1023/	Design	Therapy Scheme (mg per day)	Days of medication	n (MITT)	Indication (n)	Eradication rate (MITT)
		80/1000/1000-40	14/14/10-14	62		74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomized	PCM-P 80/1500/1500-40 ----- PC-P 80/1500-40	7/7/7/-21 14/14/-14	136 141	DU (277)	89.0 % 58.9 %
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24), GU (24)	81.3 %
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5 %
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6), HU (13) FD (11)	70.0 %

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	n (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into

the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 5 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 5: Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

- 1 Endoscopically confirmed
- 2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see Adverse Reactions). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Results, Efficacy:

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Results, Efficacy:

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets

with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Gastro-oesophageal reflux disease (GORD)
 - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - Reflux oesophagitis
- Gastrointestinal lesions refractory to H₂ blockers
- Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis
3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:
 Clarithromycin and amoxicillin or
 Clarithromycin and metronidazole or
 Amoxicillin and metronidazole
 is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see Dosage & Administration).
4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

CONTRAINDICATIONS

Pantoprazole may not be used in cases of known hypersensitivity to any components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with atazanavir (see **Interactions with other medicines**).

PRECAUTIONS

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses are at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also

observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

Impairment of fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

Interactions with other medicines

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyloestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole), might be altered due to the decrease in gastric acidity.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see **Contraindications**).

ADVERSE EFFECTS

SOMAC tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and postmarketing surveillance:

Body as a whole

Fatigue, asthenia and increased sweating

Rare reports of fever, anaphylactic reactions including anaphylactic shock and peripheral oedema

Very rare reports of substernal chest pain, increased body temperature and hot flushes

Cardiovascular disorders general

Rare reports of hypertension

Very rare reports of circulatory collapse

Central and peripheral nervous system disorders

Headache

Uncommon reports of dizziness

Very rare reports of reduced movement and speech disorder

Gastrointestinal system disorders

Diarrhoea, severe eructation, constipation or flatulence, and upper abdominal pain

Uncommon reports of nausea and vomiting

Rare reports of dry mouth, rectal disorder and colonic polyp

Very rare reports of faecal discolouration and increased saliva

Hearing and vestibular disorders

Very rare reports of tinnitus

Immune system disorders

Very rare reports of anaphylactic reactions including anaphylactic shock.

Liver and biliary system disorders

Very rare reports of increased liver enzymes (transaminases, gamma-GT) hepatic failure, cholestatic hepatitis, bilirubinaemia and jaundice

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolic and nutritional disorders

Very rare reports of hypertriglyceridaemia

Musculoskeletal

Rare reports of arthralgia

Very rare reports of myalgia and pain including skeletal pain

Renal and urinary disorders

Very rare reports of interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare reports of thrombocytopenia and increased coagulation time

Psychiatric disorders

Rare reports of onset of depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare reports of anxiety

Red and white blood cell disorders

Rare reports of anaemia

Very rare reports of leukopenia

Resistance mechanism disorders

Rare reports of sepsis

Respiratory system disorders

Very rare reports of dyspnoea

Skin and appendages

Uncommon reports of allergic reactions such as pruritus and skin rash

Very rare reports of angioedema, urticaria, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Special senses, other disorders

Metallic taste

Very rare reports of changes to the senses of smell and taste

Vascular (extracardiac) disorders

Very rare reports of flushing

Vision disorders

Uncommon reports of disturbances in vision (blurred vision)

Very rare reports of conjunctivitis

Table 6: Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 7: Adverse events (≥ 1%) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste pervasion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhea	20	13	5.2
Cough	20	13	5.2

DOSAGE AND ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see SOMAC 40 mg Granules - Instructions for use). The granules should be taken on empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H_2 -Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use***Oral administration in apple juice, orange juice or water***

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

Further information for advice on management can also be obtained from the Poisons Information Centre on 131 126 for advice about treatment and management of the overdose.

PRESENTATION AND STORAGE CONDITIONS

40 mg tablets are available in bottles of 30s and blister packs of 5s and 30s. The tablets are yellow and oval shaped, marked with the letter "P40" on one side.

20 mg tablets are available in blister packs of 30s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg granules are available in single dose sachets in packs of 5s and 30s. The granules are pale yellowish to dark brownish in colour.

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

NAME AND ADDRESS OF SPONSOR:

Nycomed Pty Ltd
ABN 71 095 610 870
2-4 Lyonpark Road
North Ryde NSW 2113

For medical enquiries, call (AUST) 1800 675 957

POISON SCHEDULE OF THE MEDICINE:

S4 – Prescription Only Medicine

TGA approval date: 19 February 2009

Date of most recent amendment: 27 October 2011

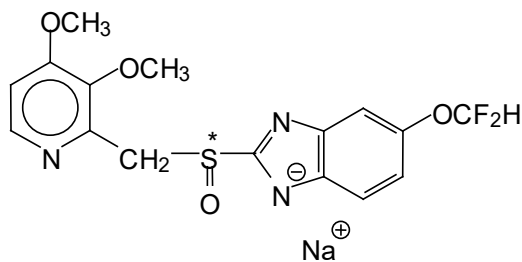
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PRODUCT INFORMATION

SOMAC[®] 40mg Injection

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole sodium
Chemical Name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide.
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	102 625-70-7 (pantoprazole)
Molecular weight:	405.5



DESCRIPTION

Pantoprazole 40 mg injection contains 42.3 mg pantoprazole sodium, 1 mg of disodium edetate, and 0.24 mg of sodium hydroxide.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder. Solubility is low at neutral pH and increases with increasing pH.

The 40 mg Injection contains the inactive ingredients disodium edetate and sodium hydroxide.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7-9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5–7 days then orally for 3–7 weeks, in the endoscopic healing of Savary-Miller stage 2–3 reflux oesophagitis (Table). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

TABLE PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

²Trials FK3005, FK3009

INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with atazanavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use:

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Genotoxicity: A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity:

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration.

Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children

To date there has been no experience with treatment in children.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see 'CONTRAINDICATIONS').

Concomitant use of proton pump inhibitors with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

ADVERSE EFFECTS

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$); not known (cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating.

Rare: fever, peripheral oedema.

Very rare: substernal chest pain and hot flushes.

Cardiovascular disorders general

Rare: hypertension.

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness.

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste.

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort.

Rare: rectal disorder and colonic polyp.

Very rare: faecal discolouration and increased saliva

Not known: severe eructation.

Hearing and vestibular disorders

Very rare: tinnitus.

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased (transaminases, gamma-GT)

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice.

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia.

Very rare: pain including skeletal pain.

Renal and urinary disorders

Very rare: interstitial nephritis.

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time.

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression (and all aggravations), hallucination, disorientation (and all aggravations) and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety.

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia.

Resistance mechanism disorders

Rare: sepsis.

Respiratory system disorders

Very rare: dyspnoea.

Reproductive system and breast disorders

Rare: gynaecomastia.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption.

Rare: angioedema and urticaria.

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity.

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis.

DOSAGE AND ADMINISTRATION

Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome 40 mg per day

Reflux oesophagitis 20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

Use in children

There are no data currently available on the use of pantoprazole in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS'). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The 40 mg injection is available as single vials.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

22 November 2006.

DATE OF MOST RECENT AMENDMENT

28 March 2013

® Registered trademark

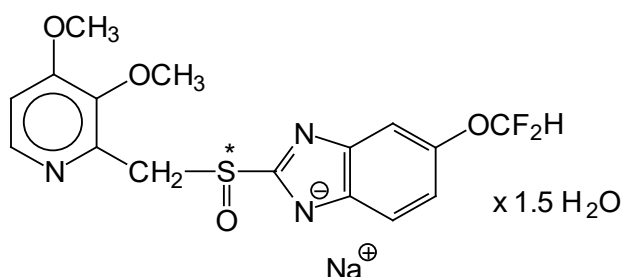
PRODUCT INFORMATION

SOMAC[®]

Tablets and Granules

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole (as pantoprazole sodium sesquihydrate)
Chemical name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	138 786-67-1 (pantoprazole sodium)
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC 40 mg enteric coated tablets contain 45.1 mg pantoprazole sodium sesquihydrate. SOMAC 20 mg enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate. SOMAC 40 mg enteric coated granules contain 45.1 mg pantoprazole sodium sesquihydrate.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

In addition to pantoprazole sodium, each unit dose sachet of granules also contains cellulose microcrystalline, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, methacrylic acid copolymer, triethyl citrate, and talc-purified.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H^+/K^+ -ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+ -ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($pH < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see 'DOSAGE & ADMINISTRATION'). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 $\mu g/mL$ following a 20 mg dose. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet

is approximately 77%. $C_{\max}$ of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and $C_{\max}$ of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), $C_{\max}$ (50%) and a delay in $T_{\max}$. This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (δ 23%) with once daily dosing.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5 to 16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

CLINICAL TRIALS

Clinical Trials in Adults

*Eradication of *H pylori**

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %

Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomized	PCM-P 80/1500/1500-40	7/7/7/-21	136	DU (277)	89.0 %
		----- PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxycillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 5 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 5: Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 'ADVERSE REACTIONS')). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the "therapeutic failure" rate after 6 months, defined as "endoscopic failure" (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least "likely" related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 6: Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
"In Remission" with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 7: Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis
- Gastrointestinal lesions refractory to H₂ blockers
- Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis
3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

Clarithromycin and amoxicillin or
Clarithromycin and metronidazole or
Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see 'DOSAGE AND ADMINISTRATION').

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.
5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with atazanavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses are at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying

histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of

pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil[®] (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see 'CONTRAINDICATIONS').

Concomitant use of proton pump inhibitors with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

ADVERSE EFFECTS

SOMAC are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients

receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

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

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased (transaminases, gamma-GT)

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression (and all aggravations), hallucination, disorientation (and all aggravations), and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria.

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 8: Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 9: Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste pervasion	45 (10.7%)	65 (10.8%)	67 (18.2%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

DOSAGE AND ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see '[SOMAC 40 mg Granules - Instructions for use](#)'). The granules should be taken on empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H_2 -Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS').

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

20 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are available in single dose sachets in packs of 5s, 28s, 30s and 84s. The granules are pale yellowish to dark brownish in colour.

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

Not all presentations and pack sizes are being distributed in Australia.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

19 February 2009

DATE OF MOST RECENT AMENDMENT

28 March 2013

® Registered trademark

Somac[®] Tablets and Granules

pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine. **You can also download the most up to date leaflet from <http://www.takedaaustralia.com.au>**.

Those updates may contain important information about the medicine and its use of which you should be aware.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking Somac against the benefits they expect it will have for you.

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 Somac is used for

Ulcers

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. When Somac is taken with antibiotics the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

Somac may also be used to prevent ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). These are medicines used to relieve pain, swelling and other symptoms of inflammation, including arthritis (inflammation of the joints).

Reflux disease

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

Zollinger-Ellison syndrome

Somac is also used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive. This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery.

SOMAC should not be given to children under 5 years of age.

There is not enough information to recommend the use of this medicine for children under the age of 5 years.

Before you take Somac

When you must not take it

Do not take Somac if you have an allergy to:

- any medicine containing pantoprazole
- any of the ingredients listed at the end of this leaflet

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the

face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not take this medicine if you have severe liver disease or cirrhosis.

Do not take Somac in combination with antibiotics or any other medicine if:

- you are allergic to any of the antibiotics or medicines your doctor may prescribe with Somac
- you have moderate to severe liver or kidney disease

Do not take Somac in combination with atazanavir (an anti-viral medication). Do not take it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to take it

Tell your doctor or pharmacist if you have any allergies **to any other medicines, foods, preservatives or dyes.**

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breast-feeding.

Your doctor can discuss the risks and benefits involved. If you have not told your doctor about any of the above, tell them before you take Somac.

Taking other medicines

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

Some medicines and Somac may interfere with each other. These include:

- warfarin - medicines used to prevent blood clots (anticoagulants)
- atazanavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer

- erlotinib or related medicines used to treat cancer

These medicines may be affected by Somac, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful with or to avoid while taking Somac.

How to take Somac

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/bottle, ask your doctor or pharmacist for help.

How much to take

The usual dose is 40 mg per day.

However, if your doctor also prescribes antibiotics in combination with Somac for the treatment of duodenal ulcers, the dose of Somac is 80 mg per day. The first 40 mg dose should be taken in the morning and the second should be taken before the evening meal for 7 days.

Your doctor will prescribe the dose that is right for you.

In children over 5 years of age, the dose of Somac for reflux oesophagitis or reflux disease is based on weight and may be 20 mg or 40 mg, depending on the condition being treated. Somac should not be taken for longer than 8 weeks.

The dose and frequency of Somac that your doctor prescribes for you depends on your medical condition.

Your doctor may change the dose as your condition changes.

How to take it

Swallow your tablets whole with a little water with or without food.

If you are using Somac granules, take it half an hour before a meal without chewing or crushing the granules. Take the granules in apple juice, orange juice or water as follows:

1. open sachet
2. sprinkle intact granules into a small volume of apple juice, pulp-free orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used
3. mix briefly just before drinking
4. drink straight away
5. to ensure that you have taken all the medicine, rinse the container thoroughly once or twice with apple juice, orange juice or water to remove any remaining granules and drink immediately

You can also take the granules in applesauce as follows:

1. open sachet
2. sprinkle intact granules on a teaspoon of applesauce.
3. swallow within 10 minutes of preparation

Somac granules are intended for people who have difficulty swallowing tablets including those who require a nasogastric tube.

When to take it

Take Somac at about the same time each day.

Taking it at the same time each day will have the best effect. It will also help you remember when to take it.

If you are taking other medicines, like antibiotics, in combination with Somac therapy, follow the instructions for the use of each medicine carefully.

Do not crush or chew the tablets or granules. Somac tablets and granules have a special coating to protect them from the acidic contents of your stomach. For Somac to work effectively, this coating must not be broken.

How long to take it

Continue taking your medicine for as long as your doctor or pharmacist tells you.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

Do not take a double dose to make up for the dose that you missed. This may increase the chance of getting an unwanted side effect.

If you are not sure what to do, ask your doctor or pharmacist.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (telephone Australia 13 11 26 or New Zealand 0800 764 766), or go to Accident and Emergency at your nearest hospital, if you or anyone else may have taken too much Somac. Do this even if there are no signs of discomfort or poisoning. Urgent medical attention may be needed.

While you are taking Somac

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking Somac.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery, tell the surgeon that you are taking this medicine.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Things you must not do

Do not use this medicine to treat any other complaints unless your doctor tells you to.

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

Things that may help your condition

Some self help measures suggested below may help your condition.

Your doctor or pharmacist can give you more information about these measures.

- **Alcohol** - your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, 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 which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** – eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **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 or pharmacist as soon as possible if you do not feel well while you are taking Somac.

It helps most people peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines have some unwanted side effects. Sometimes they are serious, but 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 or pharmacist if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- dry mouth
- metallic taste
- weakness or tiredness
- increased sweating or body temperature
- blurred vision
- skin problems such as itchiness and rash

These are the more common side effects of Somac.

Tell your doctor immediately if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- skin problems such as itchiness and rash, or swelling, blistering or peeling of the skin
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- swelling of the legs
- bleeding or bruising more easily than normal
- depression, confusion or anxiety

The above list includes serious side effects that may require medical attention. Serious side effects are rare.

Tell your doctor if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

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 Somac

Storage

Keep your tablets in their blister or bottle, and granules in their sachet pack until it is time to take them.

If you take the tablets or granules out of the blister, bottle or sachet pack they may not keep well.

Keep the medicine in a cool dry place where the temperature stays below 25°C (granules) or 30°C (tablets).

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres (5 feet) above the ground, is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or if the medicines have passed their expiry date, ask your pharmacist what to do with any tablets or granules that are left over.

Product description

What it looks like

Somac comes in 20 mg and 40 mg tablets, and 40 mg granules.

Somac 20 mg tablets - yellow and oval shaped, marked with 'P20' on one side.

Somac 40 mg tablets - yellow and oval shaped, marked with 'P40' on one side.

Somac 40 mg granules – pale yellowish to dark brownish in colour.

Somac 40 mg tablets are available in blister packs of 5 and 30 tablets and bottle packs of 30 tablets.

Somac 20 mg tablets are available in blister packs of 30 tablets.

Somac 40 mg granules are available in single aluminium foil sachets in packs of 5 and 30 sachets.

Ingredients

Tablets

Somac 40 mg tablets contain the equivalent of 40 mg pantoprazole and Somac 20 mg tablets contain the equivalent of 20 mg pantoprazole. Somac tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone
- povidone
- calcium stearate
- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode brown S-1-16530 printing ink

Granules

Somac 40 mg granules contain the equivalent of 40 mg pantoprazole.

Somac granules also contain:

- cellulose - microcrystalline
- sodium carbonate anhydrous
- crospovidone
- hypromellose
- polysorbate 80
- povidone
- titanium dioxide
- iron oxide yellow

- methacrylic acid copolymer
- triethyl citrate
- talc - purified

Somac tablets and granules do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac tablets and granules are made in Germany.

Somac tablets and granules are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

2-4 Lyonpark Road
Macquarie Park NSW 2113

Ph: 1800 675 957

The Australian Registration Number(s) are as follows:

Somac tablets (blister packs)

40 mg - AUST R 69792

20 mg - AUST R 70829

Somac tablets (bottle packs)

40 mg - AUST R 69791

Somac granules

40 mg - AUST R 148005

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This leaflet was prepared in March 2013 (Version No. 3)

Somac[®] Injection

Pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine. **You can also download the most up to date leaflet from**

<http://www.takedaaustralia.com.au>

Those updates may contain important information about the medicine and its use of which you should be aware.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac is used for

• Ulcers

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

• Reflux disease

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

• Zollinger-Ellison syndrome

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- pantoprazole
- any of the ingredients listed at the end of this leaflet

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir (an anti-viral medication). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Taking other medicines

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

Some medicines and Somac Injection may interfere with each other. These include

- warfarin - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you.

Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection. If you become pregnant while you are being given this medicine, tell your doctor immediately. **Keep all of your doctor's appointments so that your progress can be checked.**

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious,

but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- skin problems such as itchiness and rash, or swelling, blistering or peeling of the skin
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath

- high blood pressure
- swelling of the legs
- bleeding or bruising more easily than normal
- depression, confusion or anxiety

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac injection. If however, you do take your Somac injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edentate
- sodium hydroxide

Supplier

Somac Injection is made in Germany.

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park
NSW 2113
Ph: 1800 675 957

Australian Registration Number
AUST R 121427

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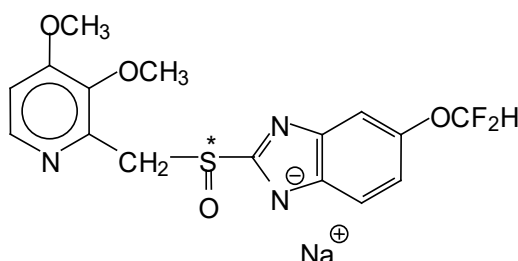
This leaflet was prepared in March 2013 (Version No.2)

PRODUCT INFORMATION

SOMAC[®] 40mg Injection

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole sodium
Chemical Name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole.
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	102 625-70-7 (pantoprazole)
Molecular weight:	405.5



Structural formula:

DESCRIPTION

Pantoprazole 40 mg injection contains 42.3 mg pantoprazole sodium, 1 mg of disodium edetate, and 0.24 mg of sodium hydroxide.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder. Solubility is low at neutral pH and increases with increasing pH.

The 40 mg Injection contains the inactive ingredients disodium edetate and sodium hydroxide.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete

pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7-9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5-7 days then orally for 3-7 weeks, in the endoscopic healing of Savary-Miller stage 2-3 reflux oesophagitis (Table). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

TABLE PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use:

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally

associated to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Genotoxicity: A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity:

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration.

Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in

humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children

To date there has been no experience with treatment in children.

Effects on ability to drive and use machines

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating.

Rare: fever, peripheral oedema.

Very rare: substernal chest pain and hot flushes.

Cardiovascular disorders general

Rare: hypertension.

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness.

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste.

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort.

Rare: rectal disorder and colonic polyp.

Very rare: faecal discolouration and increased saliva

Not known: severe eructation.

Hearing and vestibular disorders

Very rare: tinnitus.

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice.

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia.

Very rare: pain including skeletal pain.

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis.

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time.

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety.

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia.

Resistance mechanism disorders

Rare: sepsis.

Respiratory system disorders

Very rare: dyspnoea.

Reproductive system and breast disorders

Rare: gynaecomastia.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption.

Rare: angioedema and urticaria.

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity.

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis.

DOSAGE AND ADMINISTRATION

Duodenal ulcer, gastric ulcer, gastrointestinal lesions 40 mg per day
refractory to H₂ blockers, Zollinger-Ellison syndrome

Reflux oesophagitis 20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS'). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The 40 mg injection is available as single vials. Each vial contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

Store below 25°C. Keep vial in outer carton to protect from light.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

22 December 2006.

DATE OF MOST RECENT AMENDMENT

1 April 2015

® Registered trademark

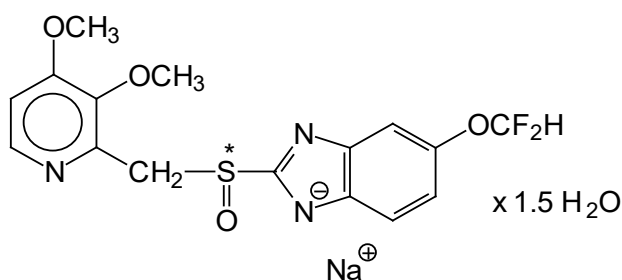
PRODUCT INFORMATION

SOMAC[®]

Tablets and Granules

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole (as pantoprazole sodium sesquihydrate)
Chemical name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	138 786-67-1 (pantoprazole sodium)
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC 40 mg enteric coated tablets contain 45.1 mg pantoprazole sodium sesquihydrate.
 SOMAC 20 mg enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate.
 SOMAC 40 mg enteric coated granules contain 45.1 mg pantoprazole sodium sesquihydrate.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

In addition to pantoprazole sodium, each unit dose sachet of granules also contains cellulose microcrystalline, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and talc-purified.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H^+/K^+ -ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+ -ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($pH < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see 'DOSAGE & ADMINISTRATION'). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in

$T_{\max}$. This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (δ 23%) with once daily dosing.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5 to 16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

CLINICAL TRIALS

Clinical Trials in Adults

Eradication of *H. pylori*

The clinical trial program of pantoprazole for eradication of *H. pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study	Design	Therapy Scheme	Days of	N	Indication	Eradication rate

BY1023		(mg per day)	medication	(MITT)	(N)	(MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %

Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomized	PCM-P 80/1500/1500-40	7/7/7/-21	136	DU (277)	89.0 %
		----- PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxycillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 5 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 5: Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

- 1 Endoscopically confirmed
- 2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 'ADVERSE REACTIONS'). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the "therapeutic failure" rate after 6 months, defined as "endoscopic failure" (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least "likely" related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 6: Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
"In Remission" with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 7: Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis
3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:
 Clarithromycin and amoxicillin or
 Clarithromycin and metronidazole or
 Amoxicillin and metronidazole
 is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see 'DOSAGE AND ADMINISTRATION').
4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.
5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole

for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses are at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was

observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

Effects on ability to drive and use machines

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

SOMAC are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion. especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria.

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 8: Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 9: Adverse events (≥ 1%) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste pervasion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

DOSAGE AND ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of

apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see '[SOMAC 40 mg Granules - Instructions for use](#)'). The granules should be taken on empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35

kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS').

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

20 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

40 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P40" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

40 mg granules are available in single dose sachets in packs of 5s, 28s, 30s and 84s. The granules are pale yellowish to dark brownish in colour. Each sachet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

Not all presentations and pack sizes are being distributed in Australia.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

8 July 1999

DATE OF MOST RECENT AMENDMENT

1 April 2015

® Registered trademark

Somac[®] Injection

Pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine. **You can also download the most up to date leaflet**

from <http://www.takedaaustralia.com.au>

Those updates may contain important information about the medicine and its use of which you should be aware.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac is used for

- **Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- **Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- **Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery. **However, do not drive a car or operate machines if**

you experience side effects such as dizziness or blurred vision.

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- **pantoprazole**
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (anti-viral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression.

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you. Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you become pregnant while you are being given this medicine, tell your doctor immediately. Keep all of your doctor's appointments so that your progress can be checked. Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth

- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness, nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness and rash, or swelling, blistering or peeling of the skin
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer)).
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium levels in your blood.
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea.

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park
NSW 2113
Ph: 1800 675 957

Australian Registration Number
AUST R 121427

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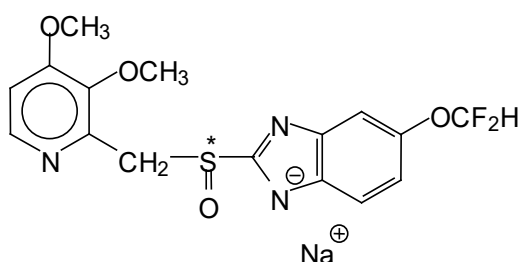
This leaflet was prepared in April 2015.

PRODUCT INFORMATION

SOMAC[®] 40mg Injection

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole sodium
Chemical Name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide.
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	138786-67-1 (pantoprazole sodium)
Molecular weight:	405.5



Structural formula:

DESCRIPTION

Pantoprazole 40 mg injection contains 42.3 mg pantoprazole sodium, 1 mg of disodium edetate, and 0.24 mg of sodium hydroxide.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder. Solubility is low at neutral pH and increases with increasing pH.

The 40 mg Injection contains the inactive ingredients disodium edetate and sodium hydroxide.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory

parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7–9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5–7 days then orally for 3–7 weeks, in the endoscopic healing of Savary-Miller stage 2–3 reflux oesophagitis (Table). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

TABLE PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use:

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally

associated to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Genotoxicity: A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity:

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration.

Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in

humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children

To date there has been no experience with treatment in children.

Effects on ability to drive and use machines

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

DOSAGE AND ADMINISTRATION

Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome 40 mg per day

Reflux oesophagitis 20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS'). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

OVERDOSAGE

There are no known symptoms of overdose in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The 40 mg injection is available as single vials. Each vial contains pantoprazole sodium equivalent to 40 mg pantoprazole.

Store below 25°C. Keep vial in outer carton to protect from light.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

22 December 2006

DATE OF MOST RECENT AMENDMENT

13 April 2016

® Registered trademark

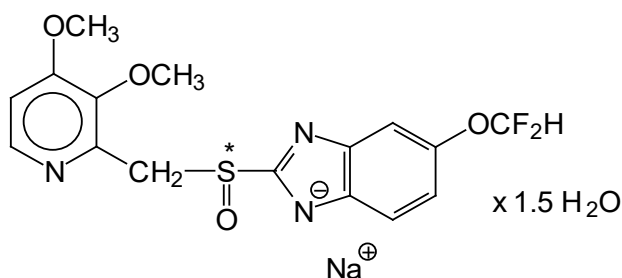
PRODUCT INFORMATION

SOMAC[®]

Tablets and Granules

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole (as pantoprazole sodium sesquihydrate)
Chemical name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S.1½ H ₂ O
CAS Number:	164579-32-2
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC 40 mg enteric coated tablets contain 45.1 mg pantoprazole sodium sesquihydrate.
SOMAC 20 mg enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate.
SOMAC 40 mg enteric coated granules contain 45.1 mg pantoprazole sodium sesquihydrate.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

In addition to pantoprazole sodium, each unit dose sachet of granules also contains microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+ -ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($pH < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see 'DOSAGE & ADMINISTRATION'). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum

and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (δ 23%) with once daily dosing.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5 to 16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

CLINICAL TRIALS

Clinical Trials in Adults

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomized	PCM-P 80/1500/1500-40	7/7/7/-21	136	DU (277)	89.0 %
		----- PC-P 80/1500-40	14/14/-14	141		58.9 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 5 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 5: Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

- 1 Endoscopically confirmed
- 2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 'ADVERSE REACTIONS'). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the "therapeutic failure" rate after 6 months, defined as "endoscopic failure" (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least "likely" related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 6: Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 7: Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis
3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

Clarithromycin and amoxicillin or
Clarithromycin and metronidazole or
Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see 'DOSAGE AND ADMINISTRATION').

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.
5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses are at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

Effects on ability to drive and use machines

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

SOMAC are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion. especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 8: Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7

Event	PCM/T* n=725	PAC n=492	PAM n=146
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 9: Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste pervasion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

DOSAGE AND ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see '[SOMAC 40 mg Granules - Instructions for use](#)'). The granules should be taken on empty stomach, at least half an hour before a meal.

In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H. pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS').

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

20 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

40 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P40" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

40 mg granules are available in single dose sachets in packs of 5s, 28s, 30s and 84s. The granules are pale yellowish to dark brownish in colour. Each sachet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

Not all presentations and pack sizes are being distributed in Australia.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

8 July 1999

DATE OF MOST RECENT AMENDMENT

13 April 2016

® Registered trademark

Somac[®] Injection

Pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac is used for

- **Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- **Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease.

This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- **Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery. **However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.**

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- pantoprazole
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (antiviral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you. Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you become pregnant while you are being given this medicine, tell your doctor immediately. Keep all of your doctor's appointments so that your progress can be checked. Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth

- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium levels in your blood
- severe and/or persistent diarrhoea, because this medicine

has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park
NSW 2113
Ph: 1800 675 957

Australian Registration Number
AUST R 121427

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This leaflet was prepared in April 2016

Somac[®] Tablets and Granules

pantoprazole

Consumer Medicine Information (CMI)

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The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking Somac against the benefits they expect it will have for you.

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 Somac is used for

Ulcers

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. When Somac is taken with antibiotics the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

Somac may also be used to prevent ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). These are medicines used to relieve pain, swelling and other symptoms of inflammation, including arthritis (inflammation of the joints).

Reflux disease

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

Zollinger-Ellison syndrome

Somac is also used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive. This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery.

However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.

Somac should not be given to children under 5 years of age.

There is not enough information to recommend the use of this medicine for children under the age of 5 years.

Before you take Somac

When you must not take it

Do not take Somac if you have an allergy to:

- any medicine containing pantoprazole
- any of the ingredients listed at the end of this leaflet

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not take this medicine if you have severe liver disease or cirrhosis.

Do not take Somac in combination with antibiotics or any other medicine if:

- you are allergic to any of the antibiotics or medicines your doctor may prescribe with Somac
- you have moderate to severe liver or kidney disease

Do not take Somac in combination with atazanavir or nelfinavir (anti-

viral medications). **Do not take it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.**

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

Before you start to take it

Tell your doctor or pharmacist if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breast-feeding.

Your doctor can discuss the risks and benefits involved. If you have not told your doctor about any of the above, tell them before you take Somac.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac.

Taking other medicines

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

Some medicines and Somac may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer

- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful with or to avoid while taking Somac.

How to take Somac

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/bottle, ask your doctor or pharmacist for help.

How much to take

The usual dose is 40 mg per day.

However, if your doctor also prescribes antibiotics in combination with Somac for the treatment of duodenal ulcers, the dose of Somac is 80 mg per day. The first 40 mg dose should be taken in the morning and the second should be taken before the evening meal for 7 days.

Your doctor will prescribe the dose that is right for you.

In children over 5 years of age, the dose of Somac for reflux oesophagitis or reflux disease is based on weight and may be 20 mg or 40 mg, depending on the condition being treated. Somac should not be taken for longer than 8 weeks.

The dose and frequency of Somac that your doctor prescribes for you depends on your medical condition.

Your doctor may change the dose as your condition changes.

How to take it

Swallow your tablets whole with a little water with or without food.

If you are using Somac granules, take it half an hour before a meal without chewing or crushing the granules. Take the granules in apple juice, orange juice or water as follows:

1. open sachet
2. sprinkle intact granules into a small volume of apple juice, pulp-free orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used
3. mix briefly just before drinking
4. drink straight away
5. to ensure that you have taken all the medicine, rinse the container thoroughly once or twice with apple juice, orange juice or water to remove any remaining granules and drink immediately

You can also take the granules in applesauce as follows:

1. open sachet
2. sprinkle intact granules on a teaspoon of applesauce.
3. swallow within 10 minutes of preparation

Somac granules are intended for people who have difficulty swallowing tablets including those who require a nasogastric tube.

When to take it

Take Somac at about the same time each day.

Taking it at the same time each day will have the best effect. It will also help you remember when to take it.

If you are taking other medicines, like antibiotics, in combination with Somac therapy, follow the instructions for the use of each medicine carefully.

Do not crush or chew the tablets or granules. Somac tablets and granules have a special coating to protect them from the acidic contents of your stomach. For Somac to work effectively, this coating must not be broken.

How long to take it

Continue taking your medicine for as long as your doctor or pharmacist tells you.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and

take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

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

This may increase the chance of getting an unwanted side effect.

If you are not sure what to do, ask your doctor or pharmacist.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (telephone Australia 13 11 26 or New Zealand 0800 764 766), or go to Accident and Emergency at your nearest hospital, if you or anyone else may have taken too much Somac. Do this even if there are no signs of discomfort or poisoning.

Urgent medical attention may be needed.

While you are taking Somac

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking Somac.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery, tell the surgeon that you are taking this medicine.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Things you must not do

Do not use this medicine to treat any other complaints unless your doctor tells you to.

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

Things that may help your condition

Some self help measures suggested below may help your condition.

Your doctor or pharmacist can give you more information about these measures.

- **Alcohol** - your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, 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 which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** – eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **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 or pharmacist as soon as possible if you do not feel well while you are taking Somac.

It helps most people peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines have some unwanted side effects. Sometimes they are serious, but 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 or pharmacist if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- dry mouth
- metallic taste
- weakness or tiredness
- increased sweating or body temperature
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

These are the more common side effects of Somac.

Tell your doctor immediately if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints

- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare.

Tell your doctor if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

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 Somac

Storage

Keep your tablets in their blister or bottle, and granules in their sachet pack until it is time to take them.

If you take the tablets or granules out of the blister, bottle or sachet pack they may not keep well.

Keep the medicine in a cool dry place where the temperature stays

below 25°C (granules) or 30°C (tablets).

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres (5 feet) above the ground, is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or if the medicines have passed their expiry date, ask your pharmacist what to do with any tablets or granules that are left over.

Product description

What it looks like

Somac comes in 20 mg and 40 mg tablets, and 40 mg granules.

Somac 20 mg tablets - yellow and oval shaped, marked with 'P20' on one side.

Somac 40 mg tablets - yellow and oval shaped, marked with 'P40' on one side.

Somac 40 mg granules – pale yellowish to dark brownish in colour.

Somac 40 mg tablets are available in blister packs of 5 and 30 tablets and bottle packs of 30 tablets.

Somac 20 mg tablets are available in blister packs of 30 tablets.

Somac 40 mg granules are available in single aluminium foil sachets in packs of 5 and 30 sachets.

Ingredients

Tablets

Somac 40 mg tablets contain the equivalent of 40 mg pantoprazole and Somac 20 mg tablets contain the equivalent of 20 mg pantoprazole. Somac tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone

- povidone
- calcium stearate
- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode brown S-1-16530 printing ink

Granules

Somac 40 mg granules contain the equivalent of 40 mg pantoprazole.

Somac granules also contain:

- –microcrystalline cellulose
- sodium carbonate anhydrous
- crospovidone
- hypromellose
- polysorbate 80
- povidone
- titanium dioxide
- iron oxide yellow
- EUDRAGIT L30D-55
- triethyl citrate
- –purified talc

Somac tablets and granules do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac tablets and granules are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

2-4 Lyonpark Road
Macquarie Park NSW 2113

Ph: 1800 675 957

The Australian Registration Number(s) are as follows:

Somac tablets (blister packs)

40 mg - AUST R 69792

20 mg - AUST R 70829

Somac tablets (bottle packs)

40 mg - AUST R 69791

Somac granules

40 mg - AUST R 148005

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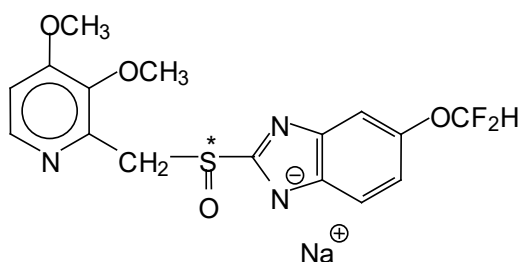
This leaflet was prepared in April 2016.

PRODUCT INFORMATION

SOMAC[®] 40mg Injection

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole sodium
Chemical Name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide.
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	138786-67-1 (pantoprazole sodium)
Molecular weight:	405.5



Structural formula:

DESCRIPTION

Pantoprazole 40 mg injection contains 42.3 mg pantoprazole sodium, 1 mg of disodium edetate, and 0.24 mg of sodium hydroxide.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder. Solubility is low at neutral pH and increases with increasing pH.

The 40 mg Injection contains the inactive ingredients disodium edetate and sodium hydroxide.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory

parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7–9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5–7 days then orally for 3–7 weeks, in the endoscopic healing of Savary-Miller stage 2–3 reflux oesophagitis (Table). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

TABLE PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use:

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally

associated to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

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 and Impairment of Fertility

Genotoxicity: A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity:

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration.

Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of

development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children

To date there has been no experience with treatment in children.

Effects on ability to drive and use machines

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

DOSAGE AND ADMINISTRATION

Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome 40 mg per day

Reflux oesophagitis 20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS'). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

OVERDOSAGE

There are no known symptoms of overdose in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The 40 mg injection is available as single vials. Each vial contains pantoprazole sodium equivalent to 40 mg pantoprazole.

Store below 25°C. Keep vial in outer carton to protect from light.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

22 December 2006

DATE OF MOST RECENT AMENDMENT

10 November 2016

® Registered trademark

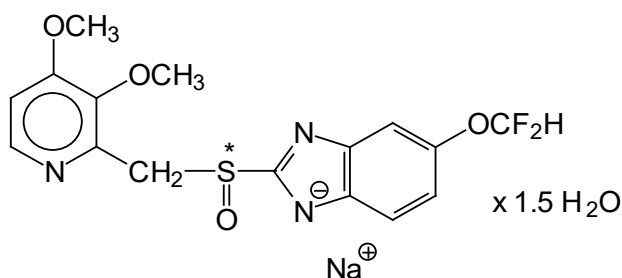
PRODUCT INFORMATION

SOMAC[®]

Tablets and Granules

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole (as pantoprazole sodium sesquihydrate)
Chemical name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S.1½ H ₂ O
CAS Number:	164579-32-2
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC 40 mg enteric coated tablets contain 45.1 mg pantoprazole sodium sesquihydrate.
SOMAC 20 mg enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate.
SOMAC 40 mg enteric coated granules contain 45.1 mg pantoprazole sodium sesquihydrate.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

In addition to pantoprazole sodium, each unit dose sachet of granules also contains microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+ -ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($pH < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see 'DOSAGE & ADMINISTRATION'). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum

and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (δ 23%) with once daily dosing.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5 to 16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

CLINICAL TRIALS

Clinical Trials in Adults

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomized	PCM-P 80/1500/1500-40	7/7/7/-21	136	DU (277)	89.0 %
		----- PC-P 80/1500-40	14/14/-14	141		58.9 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 5 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 5: Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

- 1 Endoscopically confirmed
- 2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 'ADVERSE REACTIONS'). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the "therapeutic failure" rate after 6 months, defined as "endoscopic failure" (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least "likely" related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 6: Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 7: Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis
3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

Clarithromycin and amoxicillin or
Clarithromycin and metronidazole or
Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see 'DOSAGE AND ADMINISTRATION').

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.
5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

***Clostridium difficile*:**

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

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.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses are at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids

were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found

to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

Effects on ability to drive and use machines

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

SOMAC are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion. especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 8: Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7

Event	PCM/T* n=725	PAC n=492	PAM n=146
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 9: Adverse events (≥ 1%) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste pervasion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

DOSAGE AND ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see '[SOMAC 40 mg Granules - Instructions for use](#)'). The granules should be taken on empty stomach, at least half an hour before a meal.

In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H. pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS').

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

20 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

40 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P40" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

40 mg granules are available in single dose sachets in packs of 5s, 28s, 30s and 84s. The granules are pale yellowish to dark brownish in colour. Each sachet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

Not all presentations and pack sizes are being distributed in Australia.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

8 July 1999

DATE OF MOST RECENT AMENDMENT

10 November 2016

® Registered trademark

Somac[®] Injection

Pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac is used for

- **Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- **Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease.

This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- **Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery. **However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.**

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- pantoprazole
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (antiviral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you. Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

If you become pregnant while you are being given this medicine, tell your doctor immediately. Keep all of your doctor's appointments so that your progress can be checked. Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation

- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements.

These can be a sign of low magnesium levels in your blood

- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a

white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park
NSW 2113
Ph: 1800 675 957

Australian Registration Number
AUST R 121427

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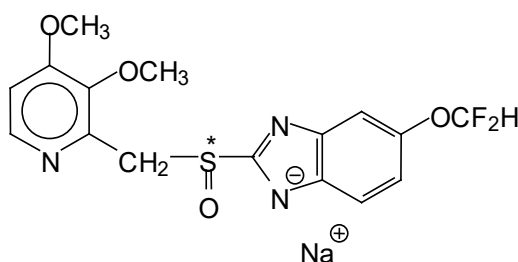
This leaflet was prepared in November 2016

PRODUCT INFORMATION

SOMAC[®] 40mg Injection

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole sodium
Chemical Name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide.
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	138786-67-1 (pantoprazole sodium)
Molecular weight:	405.5



Structural formula:

DESCRIPTION

Pantoprazole 40 mg injection contains 42.3 mg pantoprazole sodium, 1 mg of disodium edetate, and 0.24 mg of sodium hydroxide.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder. Solubility is low at neutral pH and increases with increasing pH.

The 40 mg Injection contains the inactive ingredients disodium edetate and sodium hydroxide.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory

parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7–9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5–7 days then orally for 3–7 weeks, in the endoscopic healing of Savary-Miller stage 2–3 reflux oesophagitis (Table). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

TABLE PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use:

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally

associated to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis develops.

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

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 and Impairment of Fertility

Genotoxicity: A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity:

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration.

Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of

development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children

To date there has been no experience with treatment in children.

Effects on ability to drive and use machines

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

DOSAGE AND ADMINISTRATION

Duodenal ulcer, gastric ulcer, gastrointestinal lesions 40 mg per day
refractory to H₂ blockers, Zollinger-Ellison syndrome

Reflux oesophagitis 20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS'). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

OVERDOSAGE

There are no known symptoms of overdose in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The 40 mg injection is available as single vials. Each vial contains pantoprazole sodium equivalent to 40 mg pantoprazole.

Store below 25°C. Keep vial in outer carton to protect from light.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

22 December 2006

DATE OF MOST RECENT AMENDMENT

27 April 2017

® Registered trademark

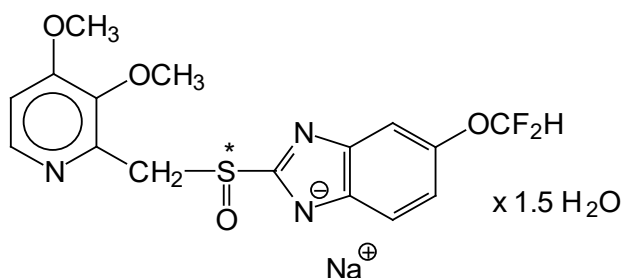
PRODUCT INFORMATION

SOMAC[®]

Tablets and Granules

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole (as pantoprazole sodium sesquihydrate)
Chemical name (CAS):	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S.1½ H ₂ O
CAS Number:	164579-32-2
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC 40 mg enteric coated tablets contain 45.1 mg pantoprazole sodium sesquihydrate.
SOMAC 20 mg enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate.
SOMAC 40 mg enteric coated granules contain 45.1 mg pantoprazole sodium sesquihydrate.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

In addition to pantoprazole sodium, each unit dose sachet of granules also contains microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+ -ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($pH < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see 'DOSAGE & ADMINISTRATION'). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum

and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (δ 23%) with once daily dosing.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5 to 16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

CLINICAL TRIALS

Clinical Trials in Adults

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomized	PCM-P 80/1500/1500-40	7/7/7/-21	136	DU (277)	89.0 %
		----- PC-P 80/1500-40	14/14/-14	141		58.9 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 5 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 5: Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

- 1 Endoscopically confirmed
- 2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 'ADVERSE REACTIONS'). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the "therapeutic failure" rate after 6 months, defined as "endoscopic failure" (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least "likely" related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 6: Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 7: Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis
3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

Clarithromycin and amoxicillin or
Clarithromycin and metronidazole or
Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see 'DOSAGE AND ADMINISTRATION').

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.
5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see 'INTERACTIONS WITH OTHER MEDICINES').

PRECAUTIONS

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

***Clostridium difficile*:**

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

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.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses are at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids

were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found

to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

Effects on ability to drive and use machines

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil[®] (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see 'CONTRAINDICATIONS').

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

SOMAC are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion. especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 8: Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7

Event	PCM/T* n=725	PAC n=492	PAM n=146
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 9: Adverse events (≥ 1%) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste pervasion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

DOSAGE AND ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see '[SOMAC 40 mg Granules - Instructions for use](#)'). The granules should be taken on empty stomach, at least half an hour before a meal.

In *H. pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H. pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see 'CONTRAINDICATIONS').

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

20 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

40 mg tablets are available in bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s and blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s. The tablets are yellow and oval shaped, marked with the letter "P40" on one side. Each tablet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

40 mg granules are available in single dose sachets in packs of 5s, 28s, 30s and 84s. The granules are pale yellowish to dark brownish in colour. Each sachet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

Not all presentations and pack sizes are being distributed in Australia.

NAME AND ADDRESS OF SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd

Level 5

2 Chifley Square

Sydney NSW 2000

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

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

8 July 1999

DATE OF MOST RECENT AMENDMENT

27 April 2017

® Registered trademark

Somac[®] Injection

Pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac is used for

- Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease.

This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery. **However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.**

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- pantoprazole
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (antiviral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you. Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

If you become pregnant while you are being given this medicine, tell your doctor immediately. Keep all of your doctor's appointments so that your progress can be checked. Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation

- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements.

These can be a sign of low magnesium levels in your blood

- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a

white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000
Ph: 1800 675 957

Australian Registration Number
AUST R 121427

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This leaflet was prepared in April 2017

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM) Injection

1 NAME OF THE MEDICINE

Pantoprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Somac 40 mg injection, each vial contains 42.3 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome</u>	40 mg per day

<u>Reflux oesophagitis</u>	20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole IV in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Check the following before use**

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was

measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

No dose adjustment is necessary in elderly patients (See Sections 4.2 Dose and Method of Administration; use in the elderly, 4.4. Special Warnings and Precautions for use; Influence on vitamin B12 absorption and 5.2 Pharmacokinetic Properties; excretion).

Paediatric use

To date there has been no experience with pantoprazole IV treatment in children.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available (see Section 5.3 Preclinical Safety Data)

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES****Mechanism of action**

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH <3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH <3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5–7 days then orally for 3–7 weeks, in the endoscopic healing of Savary-Miller stage 2–3 reflux oesophagitis (Table 1). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

Table 1 PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7–9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 40 mg Injection also contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products other than those stated in section 4.2 Dose and Method of Administration. Please also refer to Section 4.5-Interactions with other medicines and other forms of interactions

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep vial in outer carton to protect from light.

Use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

The 40 mg injection is supplied in a single clear glass vial with a grey-butyl rubber stopper and an aluminium cap.

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

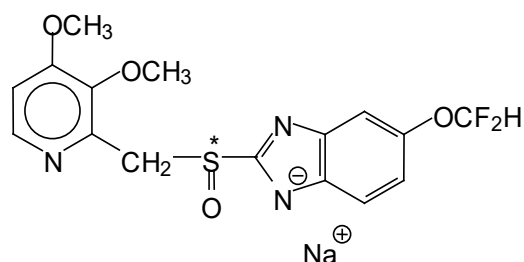
Pantoprazole sodium solubility is low at neutral pH and increases with increasing pH

Chemical structure

Chemical Name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2- pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole.

Molecular formula: C₁₆ H₁₄ F₂ N₃NaO₄S

Molecular weight: 405.5



Structural formula:

CAS number

138786-67-1 (pantoprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

22 December 2006

10 DATE OF REVISION

27 June 2018

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM SESQUIHYDRATE) Tablets and Granules

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC 20 mg enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SOMAC 40 mg enteric coated tablets, each tablet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC 40 mg enteric coated granules, each sachet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

20 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are pale yellowish to dark brownish in colour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - o Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - o Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

- Clarithromycin and amoxicillin or
- Clarithromycin and metronidazole or
- Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see section 4.2 Dose and Method of Administration).

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see 'SOMAC 40 mg Granules - Instructions for use'). The granules should be taken on an empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with Other Medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Non-steroidal anti-inflammatory drugs

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Use in the elderly

No dose adjustment is necessary in elderly patients (see Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4. Special Warnings and Precautions For Use; Influence on vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; Special populations).

Paediatric use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced foetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SOMAC tablets and granules are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 1 Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 2 Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

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

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Clinical trials In Adults

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see section 4.2 Dose And Method Of Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 3 Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind	PCM	7/7/7	121	DU (244)	73.6 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
	Randomised	80/1000/1000 ----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomised	PCM-P 80/1500/1500-40 -----	7/7/7/-21	136	DU (277)	89.0 %
		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 4 A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia

BMT bismuth/metronidazole/tetracycline
 PC pantoprazole/clarithromycin
 MITT modified intention to treat

FD functional dyspepsia
 GAS gastritis
 ERO erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 5.

Table 5 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux.

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 6. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 6 Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat).

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 7 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 7 Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included in the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 8 Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 9 Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

5.2 PHARMACOKINETIC PROPERTIES**Absorption**Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (523%) with once daily dosing.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5-16 years, AUC and C_{max} were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7- to 100- and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses is at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains; sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

Each unit dose sachet of granules also contains; microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

6.2 INCOMPATIBILITIES

Not applicable, please refer to Section 4.5-Interactions with other medicines and other forms of interactions.

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

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg and 40 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s and
- High density polyethylene (HDPE) bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s.

40 mg granules are available in:

- Plastic laminate/aluminium single dose sachets in packs of 5s, 28s, 30s and 84s.

Not all presentations and pack sizes are being distributed in Australia.

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

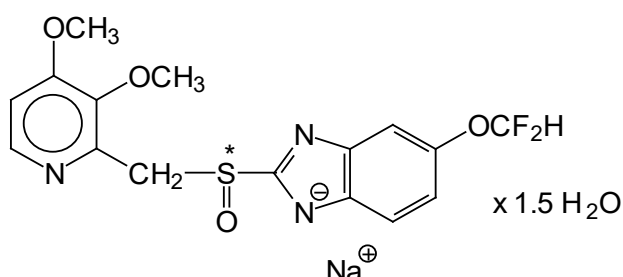
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

Molecular weight: 432.4 (sodium salt x 1.5 H_2O)

Structural formula:



CAS number

164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
 Level 5
 2 Chifley Square
 Sydney NSW 2000
 Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

27 June 2018

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM) Injection

1 NAME OF THE MEDICINE

Pantoprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Somac 40 mg injection, each vial contains 42.3 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome</u>	40 mg per day

<u>Reflux oesophagitis</u>	20–40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole IV in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C–8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Check the following before use**

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was

measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

No dose adjustment is necessary in elderly patients (See Sections 4.2 Dose and Method of Administration; use in the elderly, 4.4. Special Warnings and Precautions for use; Influence on vitamin B12 absorption and 5.2 Pharmacokinetic Properties; excretion).

Paediatric use

To date there has been no experience with pantoprazole IV treatment in children.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available (see Section 5.3 Preclinical Safety Data)

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES****Mechanism of action**

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH <3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5–7 days then orally for 3–7 weeks, in the endoscopic healing of Savary-Miller stage 2–3 reflux oesophagitis (Table 1). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

Table 1 PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7–9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 40 mg Injection also contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products other than those stated in section 4.2 Dose and Method of Administration. Please also refer to Section 4.5-Interactions with other medicines and other forms of interactions

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep vial in outer carton to protect from light.

Use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

The 40 mg injection is supplied in a single clear glass vial with a grey-butyl rubber stopper and an aluminium cap.

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

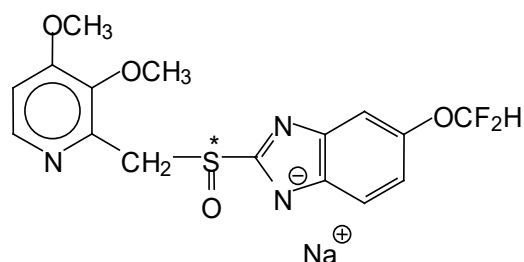
Pantoprazole sodium solubility is low at neutral pH and increases with increasing pH

Chemical structure

Chemical Name (CAS): Sodium-[5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole.

Molecular formula: C₁₆ H₁₄ F₂ N₃NaO₄S

Molecular weight: 405.5



Structural formula:

CAS number

138786-67-1 (pantoprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

22 December 2006

10 DATE OF REVISION

1 July 2019

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM SESQUIHYDRATE) Tablets and Granules

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC 20 mg enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SOMAC 40 mg enteric coated tablets, each tablet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC 40 mg enteric coated granules, each sachet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

20 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are pale yellowish to dark brownish in colour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - o Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - o Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

- Clarithromycin and amoxicillin or
- Clarithromycin and metronidazole or
- Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see section 4.2 Dose and Method of Administration).

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see 'SOMAC 40 mg Granules - Instructions for use'). The granules should be taken on an empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: - SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with Other Medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Non-steroidal anti-inflammatory drugs

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Use in the elderly

No dose adjustment is necessary in elderly patients (see Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4. Special Warnings and Precautions For Use; Influence on vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; Special populations).

Paediatric use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced foetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SOMAC tablets and granules are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 1 Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 2 Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by < 1%

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

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

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Clinical trials In Adults

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see section 4.2 Dose And Method Of Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 3 Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind	PCM	7/7/7	121	DU (244)	73.6 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
	Randomised	80/1000/1000 ----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomised	PCM-P 80/1500/1500-40 -----	7/7/7/-21	136	DU (277)	89.0 %
		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 4 A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P pantoprazole
 PAC pantoprazole/amoxicillin/clarithromycin
 PCM pantoprazole/clarithromycin/metronidazole
 PAM pantoprazole/amoxicillin/metronidazole
 PBMT pantoprazole/bismuth/metronidazole/tetracycline

DU duodenal ulcer
 GU gastric ulcer
 HU history of ulcer
 HDU history of duodenal ulcer
 NUD non ulcer dyspepsia

BMT bismuth/metronidazole/tetracycline
 PC pantoprazole/clarithromycin
 MITT modified intention to treat

FD functional dyspepsia
 GAS gastritis
 ERO erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 5.

Table 5 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux.

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 6. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 6 Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat).

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 7 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 7 Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included in the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 8 Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 9 Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

5.2 PHARMACOKINETIC PROPERTIES**Absorption**Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (523%) with once daily dosing.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5-16 years, AUC and $C_{\max}$ were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7- to 100- and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses is at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains; sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

Each unit dose sachet of granules also contains; microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

6.2 INCOMPATIBILITIES

Not applicable, please refer to Section 4.5-Interactions with other medicines and other forms of interactions.

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

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg and 40 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s and
- High density polyethylene (HDPE) bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s.

40 mg granules are available in:

- Plastic laminate/aluminium single dose sachets in packs of 5s, 28s, 30s and 84s.

Not all presentations and pack sizes are being distributed in Australia.

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

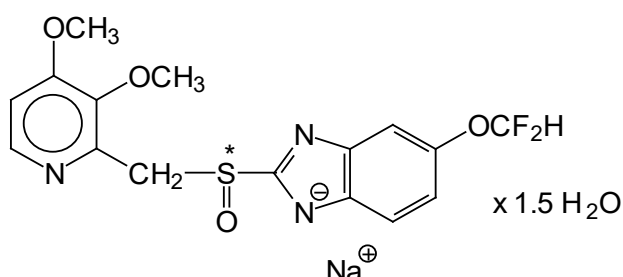
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

Molecular weight: 432.4 (sodium salt x 1.5 H_2O)

Structural formula:



CAS number

164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
 Level 5
 2 Chifley Square
 Sydney NSW 2000
 Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

1 July 2019

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)

Somac[®] Injection

pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine.

You may need to read it again.

What Somac is used for

- **Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- **Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- **Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery.

However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- pantoprazole
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (anti-viral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

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

Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system

- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you.

Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

If you become pregnant while you are being given this medicine, tell your doctor immediately. Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when

exposed to the sun, possibly with pain in the joints

- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place

away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

Level 5

2 Chifley Square

Sydney NSW 2000

Ph: 1800 675 957

Australian Registration Number
AUST R 121427

® Registered Trademark of Takeda
GmbH

This leaflet was prepared in April
2017

Somac[®] Injection

pantoprazole

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- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
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exposed to the sun, possibly with pain in the joints

- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium, calcium or potassium levels in your blood
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After using Somac

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If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

Level 5

2 Chifley Square

Sydney NSW 2000

Ph: 1800 675 957

Australian Registration Number

AUST R 121427

SOMAC® is a registered trademark
of Takeda GmbH

This leaflet was prepared in July
2020

AUSTRALIAN PRODUCT INFORMATION

SOMAC® (PANTOPRAZOLE SODIUM SESQUIHYDRATE) Tablets and Granules

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC 20 mg enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SOMAC 40 mg enteric coated tablets, each tablet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC 40 mg enteric coated granules, each sachet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

20 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are pale yellowish to dark brownish in colour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - o Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - o Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

- Clarithromycin and amoxicillin or
- Clarithromycin and metronidazole or
- Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see section 4.2 Dose and Method of Administration).

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see 'SOMAC 40 mg Granules - Instructions for use'). The granules should be taken on an empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with Other Medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Non-steroidal anti-inflammatory drugs

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Use in the elderly

No dose adjustment is necessary in elderly patients (see Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4. Special Warnings and Precautions For Use; Influence on vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; Special populations).

Paediatric use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced foetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased

pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SOMAC tablets and granules are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 1 Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 2 Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by $< 1\%$

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

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

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Clinical trials In Adults

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see section 4.2 Dose And Method Of Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 3 Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomised	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomised	PCM-P 80/1500/1500-40 -----	7/7/7/-21	136	DU (277)	89.0 %
		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxycillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 4 A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 5.

Table 5 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux.

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 6. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 6 Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat).

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 7 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 7 Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients

experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included in the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 8 Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 9 Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (523%) with once daily dosing.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5-16 years, AUC and C_{max} were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected

clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7- to 100- and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses is at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains; sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

Each unit dose sachet of granules also contains; microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

6.2 INCOMPATIBILITIES

Not applicable, please refer to Section 4.5-Interactions with other medicines and other forms of interactions.

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

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg and 40 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s and
- High density polyethylene (HDPE) bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s.

40 mg granules are available in:

- Plastic laminate/aluminium single dose sachets in packs of 5s, 28s, 30s and 84s.

Not all presentations and pack sizes are being distributed in Australia.

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

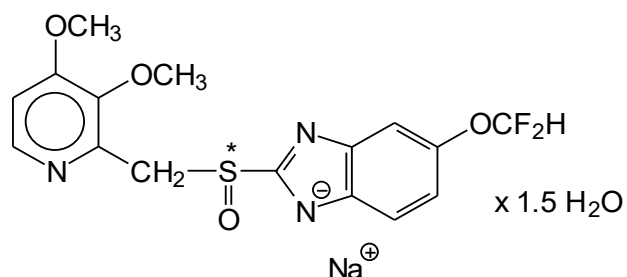
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

Molecular weight: 432.4 (sodium salt x 1.5 H₂O)

Structural formula:

**CAS number**

164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
 Level 5
 2 Chifley Square
 Sydney NSW 2000
 Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

23 July 2020

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS

SOMAC® is a registered trademark of Takeda GmbH

Somac[®] Tablets and Granules

pantoprazole

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking Somac against the benefits they expect it will have for you.

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 Somac is used for

Ulcers

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. When Somac is taken with antibiotics the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

Somac may also be used to prevent ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). These are medicines used to relieve pain, swelling and other symptoms of inflammation, including arthritis (inflammation of the joints).

Reflux disease

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

Zollinger-Ellison syndrome

Somac is also used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach

makes, to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive. This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery.

However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.

Somac should not be given to children under 5 years of age.

There is not enough information to recommend the use of this medicine for children under the age of 5 years.

Before you take Somac

When you must not take it

Do not take Somac if you have an allergy to:

- any medicine containing pantoprazole
- any of the ingredients listed at the end of this leaflet

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the

face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not take this medicine if you have severe liver disease or cirrhosis.

Do not take Somac in combination with antibiotics or any other medicine if:

- you are allergic to any of the antibiotics or medicines your doctor may prescribe with Somac
- you have moderate to severe liver or kidney disease

Do not take Somac in combination with atazanavir or nelfinavir (anti-viral medications). Do not take it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to take it

Tell your doctor or pharmacist if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breast-feeding.

Your doctor can discuss the risks and benefits involved. If you have not told your doctor about any of the above, tell them before you take Somac.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac.

Taking other medicines

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

Some medicines and Somac may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful with or to avoid while taking Somac.

How to take Somac

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/bottle, ask your doctor or pharmacist for help.

How much to take

The usual dose is 40 mg per day.

However, if your doctor also prescribes antibiotics in combination with Somac for the treatment of duodenal ulcers, the dose of Somac is 80 mg per day. The first 40 mg dose should be taken in the morning and the second should be taken before the evening meal for 7 days.

Your doctor will prescribe the dose that is right for you.

In children over 5 years of age, the dose of Somac for reflux oesophagitis or reflux disease is based on weight and may be 20 mg or 40 mg, depending on the condition being treated. Somac should not be taken for longer than 8 weeks.

The dose and frequency of Somac that your doctor prescribes for you depends on your medical condition.

Your doctor may change the dose as your condition changes.

How to take it

Swallow your tablets whole with a little water with or without food.

If you are using Somac granules, take it half an hour before a meal without chewing or crushing the granules. Take the granules in apple juice, orange juice or water as follows:

1. open sachet
2. sprinkle intact granules into a small volume of apple juice, pulp-free orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used
3. mix briefly just before drinking
4. drink straight away
5. to ensure that you have taken all the medicine, rinse the container thoroughly once or twice with apple juice, orange juice or water to remove any remaining granules and drink immediately

You can also take the granules in applesauce as follows:

1. open sachet
2. sprinkle intact granules on a teaspoon of applesauce.

- swallow within 10 minutes of preparation

Somac granules are intended for people who have difficulty swallowing tablets including those who require a nasogastric tube.

When to take it

Take Somac at about the same time each day.

Taking it at the same time each day will have the best effect. It will also help you remember when to take it.

If you are taking other medicines, like antibiotics, in combination with Somac therapy, follow the instructions for the use of each medicine carefully.

Do not crush or chew the tablets or granules. Somac tablets and granules have a special coating to protect them from the acidic contents of your stomach. For Somac to work effectively, this coating must not be broken.

How long to take it

Continue taking your medicine for as long as your doctor or pharmacist tells you.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

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

This may increase the chance of getting an unwanted side effect.

If you are not sure what to do, ask your doctor or pharmacist.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre (telephone Australia 13 11 26 or New Zealand 0800 764 766), or go to Accident and Emergency at your nearest hospital, if you or anyone else may have taken too much Somac. Do this even if there are no signs of discomfort or poisoning.

Urgent medical attention may be needed.

While you are taking Somac

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking Somac.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery, tell the surgeon that you are taking this medicine.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Things you must not do

Do not use this medicine to treat any other complaints unless your doctor tells you to.

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

Things that may help your condition

Some self help measures suggested below may help your condition. Your doctor or pharmacist can give you more information about these measures.

- **Alcohol –**
your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, 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 which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits –**
eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **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 or pharmacist as soon as possible if you do not feel well while you are taking Somac.

It helps most people peptic ulcers or reflux disease, but it may have

unwanted side effects in a few people.

All medicines have some unwanted side effects. Sometimes they are serious, but 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 or pharmacist if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- dry mouth
- metallic taste
- weakness or tiredness
- increased sweating or body temperature
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

These are the more common side effects of Somac.

Tell your doctor immediately if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine
- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints
- swelling of the face, lips, mouth, tongue or throat which may cause

difficulty in swallowing or breathing

- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium, calcium or potassium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare.

Tell your doctor if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

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 Somac

Storage

Keep your tablets in their blister or bottle, and granules in their sachet pack until it is time to take them.

If you take the tablets or granules out of the blister, bottle or sachet pack they may not keep well.

Keep the medicine in a cool dry place where the temperature stays below 25°C (granules) or 30°C (tablets).

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres (5 feet) above the ground, is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or if the medicines have passed their expiry date, ask your pharmacist what to do with any tablets or granules that are left over.

Product description

What it looks like

Somac comes in 20 mg and 40 mg tablets, and 40 mg granules.

Somac 20 mg tablets - yellow and oval shaped, marked with 'P20' on one side.

Somac 40 mg tablets - yellow and oval shaped, marked with 'P40' on one side.

Somac 40 mg granules – pale yellowish to dark brownish in colour.

Somac 40 mg tablets are available in blister packs of 5 and 30 tablets and bottle packs of 30 tablets.

Somac 20 mg tablets are available in blister packs of 30 tablets.

Somac 40 mg granules are available in single aluminium foil sachets in packs of 5 and 30 sachets.

Ingredients

Tablets

Somac 40 mg tablets contain the equivalent of 40 mg pantoprazole and Somac 20 mg tablets contain the equivalent of 20 mg pantoprazole. Somac tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone
- povidone
- calcium stearate
- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode brown S-1-16530 printing ink

Granules

Somac 40 mg granules contain the equivalent of 40 mg pantoprazole.

Somac granules also contain:

- microcrystalline cellulose
- sodium carbonate anhydrous
- crospovidone
- hypromellose
- polysorbate 80
- povidone
- titanium dioxide
- iron oxide yellow
- EUDRAGIT L30D-55
- triethyl citrate
- purified talc

Somac tablets and granules do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac tablets and granules are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

Level 5

2 Chifley Square

Sydney NSW 2000

Ph: 1800 675 957

The Australian Registration Number(s) are as follows:

Somac tablets (blister packs)

40 mg - AUST R 69792

20 mg - AUST R 70829

Somac tablets (bottle packs)

40 mg - AUST R 69791

Somac granules

40 mg - AUST R 148005

SOMAC® is a registered trademark of Takeda GmbH

This leaflet was prepared in June 2020.

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM) Injection

1 NAME OF THE MEDICINE

Pantoprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Somac 40 mg injection, each vial contains 42.3 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome</u>	40 mg per day
<u>Reflux oesophagitis</u>	20-40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole IV in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Check the following before use**

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice

and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

No dose adjustment is necessary in elderly patients (See Sections 4.2 Dose and Method of Administration; use in the elderly, 4.4. Special Warnings and Precautions for use; Influence on vitamin B12 absorption and 5.2 Pharmacokinetic Properties; excretion).

Paediatric use

To date there has been no experience with pantoprazole IV treatment in children.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available (see Section 5.3 Preclinical Safety Data)

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES****Mechanism of action**

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH <3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH <3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal

cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5-7 days then orally for 3-7 weeks, in the endoscopic healing of Savary-Miller stage 2-3 reflux oesophagitis (Table 1). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

Table 1 PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

²Trials FK3005, FK3009

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h.

Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half-life increased from 1 h to 7-9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were

detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 40 mg Injection also contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products other than those stated in section 4.2 Dose and Method of Administration. Please also refer to Section 4.5-Interactions with other medicines and other forms of interactions

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep vial in outer carton to protect from light.

Use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

The 40 mg injection is supplied in a single clear glass vial with a grey-butyl rubber stopper and an aluminium cap.

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

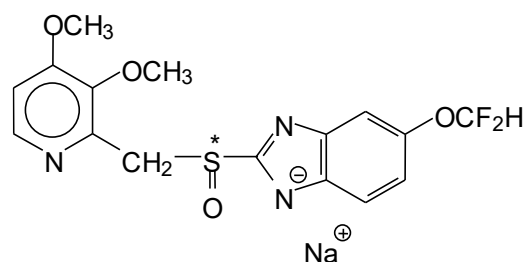
Pantoprazole sodium solubility is low at neutral pH and increases with increasing pH

Chemical structure

Chemical Name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2- pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolidine.

Molecular formula: C₁₆ H₁₄ F₂ N₃NaO₄S

Molecular weight: 405.5



Structural formula:

CAS number

138786-67-1 (pantoprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

22 December 2006

10 DATE OF REVISION

6 July 2020

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS

SOMAC® is a registered trademark of Takeda GmbH

AUSTRALIAN PRODUCT INFORMATION

SOMAC® (PANTOPRAZOLE SODIUM SESQUIHYDRATE) Tablets and Granules

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC 20 mg enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SOMAC 40 mg enteric coated tablets, each tablet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC 40 mg enteric coated granules, each sachet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

20 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are pale yellowish to dark brownish in colour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - o Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - o Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

- Clarithromycin and amoxicillin or
- Clarithromycin and metronidazole or
- Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see section 4.2 Dose and Method of Administration).

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see 'SOMAC 40 mg Granules - Instructions for use'). The granules should be taken on an empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with Other Medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Non-steroidal anti-inflammatory drugs

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Use in the elderly

No dose adjustment is necessary in elderly patients (see Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4. Special Warnings and Precautions For Use; Influence on vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; Special populations).

Paediatric use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced foetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased

pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SOMAC tablets and granules are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 1 Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 2 Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by $< 1\%$

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

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

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Clinical trials In Adults

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see section 4.2 Dose And Method Of Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 3 Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomised	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomised	PCM-P 80/1500/1500-40 -----	7/7/7/-21	136	DU (277)	89.0 %
		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxycillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 4 A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 5.

Table 5 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux.

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 6. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 6 Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat).

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 7 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 7 Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients

experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included in the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 8 Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 9 Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (523%) with once daily dosing.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5-16 years, AUC and C_{max} were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected

clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7- to 100- and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses is at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains; sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

Each unit dose sachet of granules also contains; microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

6.2 INCOMPATIBILITIES

Not applicable, please refer to Section 4.5-Interactions with other medicines and other forms of interactions.

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

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg and 40 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s and
- High density polyethylene (HDPE) bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s.

40 mg granules are available in:

- Plastic laminate/aluminium single dose sachets in packs of 5s, 28s, 30s and 84s.

Not all presentations and pack sizes are being distributed in Australia.

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

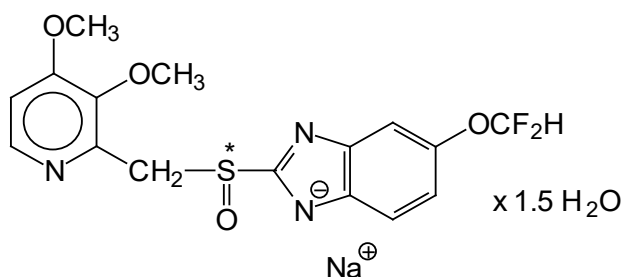
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

Molecular weight: 432.4 (sodium salt x 1.5 H₂O)

Structural formula:

**CAS number**

164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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 Sydney NSW 2000
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9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

19 November 2020

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS
8	Revision of sponsor address details and addition of sponsor website

SOMAC® is a registered trademark of Takeda GmbH

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM) Injection

1 NAME OF THE MEDICINE

Pantoprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Somac 40 mg injection, each vial contains 42.3 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome</u>	40 mg per day
<u>Reflux oesophagitis</u>	20-40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole IV in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Check the following before use**

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice

and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

No dose adjustment is necessary in elderly patients (See Sections 4.2 Dose and Method of Administration; use in the elderly, 4.4. Special Warnings and Precautions for use; Influence on vitamin B12 absorption and 5.2 Pharmacokinetic Properties; excretion).

Paediatric use

To date there has been no experience with pantoprazole IV treatment in children.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available (see Section 5.3 Preclinical Safety Data)

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH <3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH <3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal

cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5-7 days then orally for 3-7 weeks, in the endoscopic healing of Savary-Miller stage 2-3 reflux oesophagitis (Table 1). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

Table 1 PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

²Trials FK3005, FK3009

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h.

Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half-life increased from 1 h to 7-9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were

detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 40 mg Injection also contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products other than those stated in section 4.2 Dose and Method of Administration. Please also refer to Section 4.5-Interactions with other medicines and other forms of interactions

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep vial in outer carton to protect from light.

Use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

The 40 mg injection is supplied in a single clear glass vial with a grey-butyl rubber stopper and an aluminium cap.

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

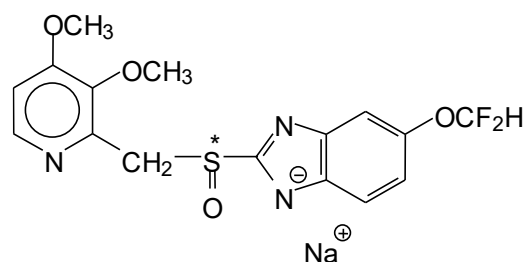
Pantoprazole sodium solubility is low at neutral pH and increases with increasing pH

Chemical structure

Chemical Name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole.

Molecular formula: C₁₆ H₁₄ F₂ N₃NaO₄S

Molecular weight: 405.5



Structural formula:

CAS number

138786-67-1 (pantoprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
 Level 39
 225 George Street
 Sydney NSW 2000
 Australia
 Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

22 December 2006

10 DATE OF REVISION

25 November 2020

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS
8	Revision of sponsor address details and addition of sponsor website

SOMAC® is a registered trademark of Takeda GmbH

Somac[®] Injection

pantoprazole sodium

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine.

You may need to read it again.

What Somac is used for

- **Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- **Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- **Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery.

However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- **pantoprazole**
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (anti-viral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

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

Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system

- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you.

Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

If you become pregnant while you are being given this medicine, tell your doctor immediately.

Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Tell your doctor if your reflux symptoms return after you stop taking this medicine.

The symptoms of reflux may return after stopping this medicine suddenly, especially if you have taken it for a while.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever,

itching, yellowing of the skin and eyes, and dark coloured urine

- blood in the urine
- increased or decreased need to urinate
- skin problems such as itchiness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints and general fever
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps. These can be a sign of low magnesium, calcium or potassium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole sodium.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

Level 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

Australian Registration Number
AUST R 121427

SOMAC® is a registered trademark
of Takeda GmbH

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AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] (PANTOPRAZOLE SODIUM) Injection

1 NAME OF THE MEDICINE

Pantoprazole sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Somac 40 mg injection, each vial contains 42.3 mg pantoprazole sodium equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

Pantoprazole sodium is a white to off-white amorphous hygroscopic powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note. Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with anti-microbial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H₂ blockers, Zollinger-Ellison syndrome</u>	40 mg per day

<u>Reflux oesophagitis</u>	20-40 mg per day

Intravenous Somac should be replaced with oral therapy as soon as practicable.

Preparation for use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 12 hours stored at 2–8°C, and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

This product must not be mixed with other medicinal products other than those stated above.

Use in children

There are no data currently available on the use of pantoprazole IV in children.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications). With milder forms of liver disease, the initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

This product contains no antimicrobial agent. Somac injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Check the following before use**

The intravenous administration of Somac injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Influence on vitamin B12 absorption

In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if respective clinical symptoms are observed.

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice

and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

No dose adjustment is necessary in elderly patients (See Sections 4.2 Dose and Method of Administration; use in the elderly, 4.4. Special Warnings and Precautions for use; Influence on vitamin B12 absorption and 5.2 Pharmacokinetic Properties; excretion).

Paediatric use

To date there has been no experience with pantoprazole IV treatment in children.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available (see Section 5.3 Preclinical Safety Data)

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Somac injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H. pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Common: Injection site thrombophlebitis

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema

Very rare: substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the oral administration of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (TIN) (with possible progression to renal failure)

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence.

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema and urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome; and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES****Mechanism of action**

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH <3 and 4 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH <3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal

cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5-7 days then orally for 3-7 weeks, in the endoscopic healing of Savary-Miller stage 2-3 reflux oesophagitis (Table 1). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

Table 1 PANTOPRAZOLE 40 mg/day (IV plus oral) IN ENDOSCOPIC HEALING OF STAGE 2-3 OESOPHAGITIS (Intention to treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

²Trials FK3005, FK3009

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h.

Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half-life increased from 1 h to 7-9 h in patients with liver cirrhosis compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were

detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 40 mg Injection also contains 1 mg disodium edetate and 0.24 mg sodium hydroxide.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products other than those stated in section 4.2 Dose and Method of Administration. Please also refer to Section 4.5-Interactions with other medicines and other forms of interactions

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep vial in outer carton to protect from light.

Use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C-8°C for not more than 12 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

The 40 mg injection is supplied in a single clear glass vial with a grey-butyl rubber stopper and an aluminium cap.

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

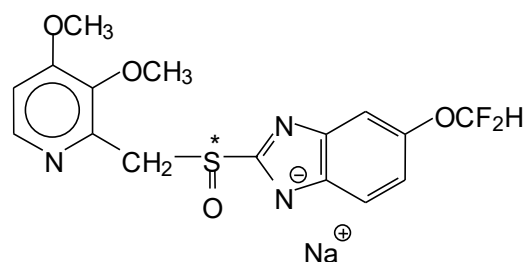
Pantoprazole sodium solubility is low at neutral pH and increases with increasing pH

Chemical structure

Chemical Name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole.

Molecular formula: C₁₆ H₁₄ F₂ N₃NaO₄S

Molecular weight: 405.5



Structural formula:

CAS number

138786-67-1 (pantoprazole sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
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9 DATE OF FIRST APPROVAL

22 December 2006

10 DATE OF REVISION

29 April 2021

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS
8	Revision of sponsor address details and addition of sponsor website
4.8	Revision of AE, tubulointerstitial nephritis

SOMAC® is a registered trademark of Takeda GmbH

AUSTRALIAN PRODUCT INFORMATION

SOMAC® (PANTOPRAZOLE SODIUM SESQUIHYDRATE) Tablets and Granules

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC 20 mg enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SOMAC 40 mg enteric coated tablets, each tablet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC 40 mg enteric coated granules, each sachet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

20 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are pale yellowish to dark brownish in colour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - o Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - o Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

- Clarithromycin and amoxicillin or
- Clarithromycin and metronidazole or
- Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see section 4.2 Dose and Method of Administration).

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.
5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see 'SOMAC 40 mg Granules - Instructions for use'). The granules should be taken on an empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with Other Medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Non-steroidal anti-inflammatory drugs

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Use in the elderly

No dose adjustment is necessary in elderly patients (see Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4. Special Warnings and Precautions For Use; Influence on vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; Special populations).

Paediatric use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced foetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased

pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SOMAC tablets and granules are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (TIN) (with possible progression to renal failure)

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 1 Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 2 Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by $< 1\%$

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

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

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Clinical trials In Adults

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see section 4.2 Dose And Method Of Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 3 Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomised	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomised	PCM-P 80/1500/1500-40 -----	7/7/7/-21	136	DU (277)	89.0 %
		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 4 A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 5.

Table 5 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux.

Data Set	1 week			2 weeks		
	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 6. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 6 Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat).

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 7 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 7 Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients

experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included in the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 8 Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 9 Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (523%) with once daily dosing.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5-16 years, AUC and C_{max} were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected

clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7- to 100- and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses is at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains; sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

Each unit dose sachet of granules also contains; microcrystalline cellulose, sodium carbonate anhydrous, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

6.2 INCOMPATIBILITIES

Not applicable, please refer to Section 4.5-Interactions with other medicines and other forms of interactions.

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

SOMAC tablets in bottles or blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg and 40 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s and
- High density polyethylene (HDPE) bottles of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 90s, 100s, 140s, 280s, 700s.

40 mg granules are available in:

- Plastic laminate/aluminium single dose sachets in packs of 5s, 28s, 30s and 84s.

Not all presentations and pack sizes are being distributed in Australia.

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

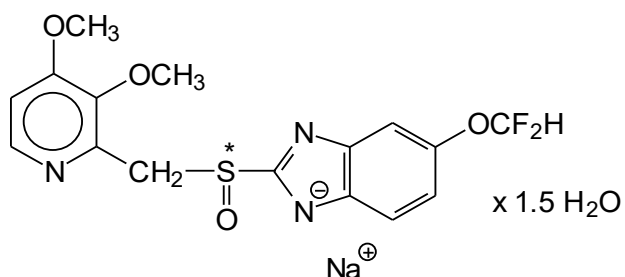
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

Molecular weight: 432.4 (sodium salt x 1.5 H₂O)

Structural formula:

**CAS number**

164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

29 April 2021

Summary table of changes

Section changed	Summary of new information
All	Reformatting PI and – minor editorial changes
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
6.5	Addition of container closure information
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS
8	Revision of sponsor address details and addition of sponsor website
4.8	Revision of AE, tubulointerstitial nephritis

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Somac[®] Injection

pantoprazole sodium

Consumer Medicine Information (CMI)

What is in this leaflet

This leaflet answers some common questions about Somac.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

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

Keep this leaflet with the medicine.

You may need to read it again.

What Somac is used for

- **Ulcers**

Somac is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

- **Reflux disease**

Somac is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Somac is also used to prevent reflux oesophagitis from coming back.

- **Zollinger-Ellison syndrome**

Somac is used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms and allow healing to take place.

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

Your doctor may have prescribed it for another purpose.

This medicine is not addictive.

This medicine is available only with a doctor's prescription.

This medicine is not expected to affect your ability to drive a car or operate machinery.

However, do not drive a car or operate machines if you experience side effects such as dizziness or blurred vision.

Before you use Somac

When you must not use it

Do not use Somac if you have an allergy to:

- **pantoprazole**
- **any of the ingredients listed at the end of this leaflet**

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not use Somac if you have severe liver disease or cirrhosis.

Do not use Somac in combination with atazanavir or nelfinavir (anti-viral medications). Do not give Somac injection to children.

Safety and effectiveness in children have not been established.

Do not use it after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to use it

Tell your doctor if you have any allergies to any other medicines, foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breastfeeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor about any of the above, tell them before you use Somac Injection.

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take Somac Injection.

Taking other medicines

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

Some medicines and Somac Injection may interfere with each other. These include

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil - medicines used to suppress the immune system

- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Injection, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor has more information on medicines to be careful with or to avoid while taking Somac Injection.

How to use Somac Injection

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.

How much to use and when to use it

The dose and frequency of your Somac Injection will be determined by your doctor and will depend on your medical condition. Your doctor may change the dose as your condition changes.

How to use it

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

How long to use it

Continue using your medicine for as long as your doctor tells you.

Your doctor will determine how long you need to be treated with Somac Injection.

If a dose is missed

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If too much is given (overdose)

Your doctor will ensure that you receive the correct dose of Somac Injection.

Never administer this medicine to yourself.

Overdose is unlikely with Somac. However it may cause an increase in side effects. (The side effects are listed under the heading, 'Side effects' in this leaflet.)

While you are using Somac Injection

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are being treated with Somac Injection.

Tell any other doctors, dentists and pharmacists who treat you that you are being given Somac Injection.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

If you become pregnant while you are being given this medicine, tell your doctor immediately.

Keep all of your doctor's appointments so that your progress can be checked.

Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Tell your doctor if your reflux symptoms return after you stop taking this medicine.

The symptoms of reflux may return after stopping this medicine suddenly, especially if you have taken it for a while.

Side effects

Tell your doctor as soon as possible if you do not feel well while you are given Somac Injection. All medicines have some unwanted side effects. Sometimes they are serious, but 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 this list of possible side effects. You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

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

- headache
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel
- indigestion
- constipation
- increased sweating or body temperature
- dry mouth
- pain and swelling at the site of injection
- dizziness
- weakness or tiredness
- metallic taste
- blurred vision
- skin problems such as itchiness and rash
- trouble sleeping

The above list includes the more common side effects of your medicine. They are usually mild and short-lived.

Tell your doctor as soon as possible if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever,

itching, yellowing of the skin and eyes, and dark coloured urine

- blood in the urine
- increased or decreased need to urinate
- severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints and general fever
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- water retention, swelling
- bleeding or bruising more easily than normal
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps. These can be a sign of low magnesium, calcium or potassium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare. Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people. Some of these side effects can only be found when your doctor does tests from time to time to check your progress.

After using Somac

Storage

Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to store it in a safe place away from heat (below 25°C) and away from light. Do not leave your Somac Injection in a car.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When taking Somac Injection at home, always ensure that it is stored in a place where children cannot reach it i.e. a locked cupboard at least one-and-a-half meters (5 feet) above the ground is a good place to store medicine.

Disposal

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Product description

What it looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Ingredients

The active ingredient in Somac Injection is pantoprazole sodium.

The inactive ingredients are:

- disodium edetate
- sodium hydroxide

Supplier

Somac Injection is supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

Level 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

Australian Registration Number
AUST R 121427

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2022

Consumer Medicine Information (CMI) summary

The [full CMI](#) on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using SOMAC Injection?

SOMAC Injection contains the active ingredient pantoprazole sodium. SOMAC Injection is used to treat and help heal duodenal and gastric ulcers. SOMAC Injection is also used to treat reflux oesophagitis or reflux disease and can be used to prevent reflux oesophagitis from coming back. SOMAC Injection is also used to treat a rare condition called Zollinger-Ellison syndrome. For more information, see Section [1. Why am I using SOMAC injection?](#) in the full CMI.

2. What should I know before I use SOMAC Injection?

Do not use if you have ever had an allergic reaction to pantoprazole or any of the ingredients listed at the end of the CMI. **Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding. Tell your doctor if you have severe liver disease or cirrhosis.**

For more information, see Section [2. What should I know before I use SOMAC Injection?](#) in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with SOMAC Injection and affect how it works. A list of these medicines is in Section [3. What if I am taking other medicines?](#) in the full CMI.

4. How do I use SOMAC Injection?

The dose and frequency of SOMAC Injection that your doctor prescribes for you depends on your medical condition. Your doctor may change the dose as your condition changes. Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist. More instructions can be found in Section [4. How do I use SOMAC Injection?](#) in the full CMI.

5. What should I know while using SOMAC Injection?

Things you should do	- Remind any doctor, dentist or pharmacist you visit that you are using SOMAC Injection. - Tell your doctor if you are pregnant or plan to become pregnant or are breastfeeding.
Things you should not do	- Do not stop using SOMAC Injection without talking to your doctor first. - Do not use SOMAC Injection to treat any other complaints unless your doctor tells you to. - Do not give SOMAC Injection to anyone else, even if they have the same symptoms as you.
Driving or using machines	Do not drive or operate machinery if SOMAC Injection affects your ability to concentrate and react.
Drinking alcohol	Your doctor may advise you to limit your alcohol intake to help your condition.
Looking after your medicine	Keep SOMAC Injection in a cool place where the temperature stays below 25°C. Keep the vial in the outer carton to protect from light.

For more information, see Section [5. What should I know while using SOMAC Injection?](#) in the full CMI.

6. Are there any side effects?

Headache, dizziness, diarrhoea, nausea or vomiting, stomach pain, excessive gas in stomach or bowel, indigestion, constipation, sore breasts, dry mouth, taste disturbances, metallic taste, weakness/ tiredness, trouble sleeping, pain and swelling at the site of injection, increased sweating/body temperature, blurred vision, skin problems, unusual tiredness or weakness, tingling or numbness, blood in urine, increased or decreased need to urinate, frequent infections, chest pain, high blood pressure, irregular heartbeat, water retention, swelling, bleeding/bruising more easily than normal, depression, confusion or anxiety, bone fracture of hip, wrist or spine, seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps, severe and/or persistent diarrhoea. Signs of liver inflammation including yellowing of skin/eyes, nausea, vomiting, loss of appetite, feeling unwell, fever, itching and dark coloured urine; severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of skin or rash when exposed to sun, possibly with pain in joints and general fever; swelling of face, lips, mouth, tongue or throat which may cause difficulty swallowing or breathing; shortness of breath, wheezing or difficulty breathing; black stools; vomiting blood. For more information, including what to do if you have any side effects, see Section [6. Are there any side effects?](#) in the full CMI.

Somac[®] Injection

Active ingredient(s): *pantoprazole sodium*

Consumer Medicine Information (CMI)

This leaflet provides important information about using SOMAC Injection. It does not take the place of talking to your doctor or pharmacist. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using SOMAC Injection.**

Where to find information in this leaflet:

1. [Why am I using SOMAC Injection?](#)
2. [What should I know before I use SOMAC Injection?](#)
3. [What if I am taking other medicines Injection?](#)
4. [How do I use SOMAC Injection?](#)
5. [What should I know while using SOMAC Injection?](#)
6. [Are there any side effects?](#)
7. [Product details](#)

1. Why am I using SOMAC Injection?

SOMAC Injection contains the active ingredient pantoprazole sodium. SOMAC Injection belongs to a group of medicines called proton pump inhibitors (PPIs). SOMAC Injection works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place.

Ulcers

SOMAC Injection is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

Reflux disease

SOMAC Injection is also used to treat reflux oesophagitis or reflux disease. This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

SOMAC Injection is also used to prevent reflux oesophagitis from coming back.

Zollinger-Ellison syndrome

SOMAC Injection is also used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

2. What should I know before I use SOMAC Injection?

Warnings

Do not take SOMAC Injection if:

- you are allergic to pantoprazole sodium, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicines containing proton pump inhibitors.
- always check the ingredients to make sure you can use this medicine.
- symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, rash, itching or hives on the skin.
- you have severe liver disease or cirrhosis.
- after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering. If it has expired or is damaged return it to your pharmacist for disposal.

Do not take SOMAC Injection in combination with atazanavir or nelfinavir (anti-viral medications).

Do not give SOMAC Injection to children under 5 years of age. There is not enough information to recommend the use of this medicine for children under the age of 5 years.

Check with your doctor if you:

- you have any allergies to any other medicines, foods, preservatives or dyes
- have reduced body stores or risk factors for reduced vitamin B12, as pantoprazole may lead to a reduced absorption of vitamin B12
- have any other medical conditions
- take any medicines for any other condition

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take SOMAC Injection.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section [6. Are there any side effects?](#)

Pregnancy and breastfeeding

Check with your doctor if you are pregnant or intend to become pregnant. It is not known if it is safe for you to take SOMAC Injection while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed. It is not known if your baby can take in SOMAC Injection from breast milk if you are breastfeeding.

Ask your doctor about the risks and benefits involved.

3. What if I am taking other medicines?

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

Do not take SOMAC Injection in combination with atazanavir or nelfinavir (anti-viral medications).

Some medicines and SOMAC Injection may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by SOMAC Injection or may affect how well it works. You may need to use different amounts of your medicine or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful with or to avoid while taking SOMAC Injection.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect SOMAC Injection.

4. How do I use SOMAC Injection?

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, ask your doctor or pharmacist for help.

How much to take

The dose and frequency of SOMAC Injection that your doctor prescribes for you depends on your medical condition.

Your doctor may change the dose as your condition changes.

When to take SOMAC Injection

Your doctor will determine when you are to be given Somac Injection.

How to take SOMAC Injection

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

Your doctor will determine how long you need to be treated with Somac Injection.

SOMAC Injection is intended for people who are unable to take tablets or granules.

If you forget to take SOMAC Injection

SOMAC Injection should be used regularly at the same time each day.

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If you take too much SOMAC Injection

If you think that you have been given too much SOMAC Injection, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (by calling 13 11 26), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using SOMAC Injection?

Things you should do

- **If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking SOMAC Injection.**
- **Tell any other doctors, dentists and pharmacists who treat you that you are taking SOMAC Injection.**
- **If you are going to have surgery, tell the surgeon that you are taking SOMAC Injection.**
- **If you become pregnant while you are taking SOMAC Injection, tell your doctor or pharmacist immediately.**
- **If you are about to have any blood tests, tell your doctor that you are taking SOMAC Injection.** It may interfere with the results of some tests.
- **Keep all of your doctor's appointments so that your progress can be checked.** Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.
- **Tell your doctor if your reflux symptoms return after you stop taking this medicine.** The symptoms of reflux may return after stopping this medicine suddenly, especially if you have taken it for a while.

Things you should not do

- Do not use SOMAC Injection to treat any other complaints unless your doctor tells you to.
- Do not give SOMAC Injection to anyone else, even if they have the same symptoms as you.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how SOMAC Injection affects you. A small number of patients have felt dizzy or had problems with their vision after taking SOMAC.

Things that may help your condition

Some self-help measures suggested below may help your condition. Your doctor or pharmacist can give you more information about these measures.

- **Alcohol** – your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, 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 which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** – eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **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.

Looking after your medicine

- Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to keep SOMAC Injection in a cool place where the temperature stays below 25°C. Keep the vial in the outer carton to protect from light.
- Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car. 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.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When to discard your medicine

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
• headache • dizziness • diarrhoea • nausea or vomiting • stomach pain • excessive gas in the stomach or bowel • indigestion • constipation • sore breasts • dry mouth • metallic taste • taste disturbances • weakness or tiredness • trouble sleeping • pain and swelling at the site of injection	Speak to your doctor if you have any of these less serious side effects and they worry you.
• increased sweating or body temperature • blurred vision • skin problems such as itchiness and rash • unusual tiredness or weakness • tingling or numbness ("pins and needles") • blood in the urine • increased or decreased need to urinate • frequent infections such as fever, severe chills, sore throat or mouth ulcers • chest pain • high blood pressure • irregular (fast or slow) heartbeat • water retention, swelling • bleeding or bruising more easily than normal • depression, confusion or anxiety • bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or	Speak to your doctor immediately if you have any of these side effects. These side effects may require medical attention.

Less serious side effects	What to do
use them long term (a year or longer)) - symptoms such as seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps. These can be a sign of low magnesium, calcium or potassium levels in your blood - severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea	

Serious side effects

Serious side effects	What to do
- signs of liver inflammation including yellowing of the skin or eyes, nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching and dark coloured urine - severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints and general fever - swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing - shortness of breath, wheezing or difficulty breathing - black (blood stained) stools - vomiting blood	Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What SOMAC Injection contains

Active ingredient (main ingredient)	pantoprazole sodium
Other ingredients (inactive ingredients)	- disodium edetate - sodium hydroxide

Do not take this medicine if you are allergic to any of these ingredients.

Somac Injection does not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

What SOMAC Injection looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Australian Registration Number

AUST R 121427

Who distributes SOMAC Injection

Takeda Pharmaceuticals Australia Pty Ltd

Level 39

225 George Street

Sydney NSW 2000

Australia

Telephone: 1800 012 612

www.takeda.com/en-au

This leaflet was prepared in May 2025.

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AUSTRALIAN PRODUCT INFORMATION

SOMAC® (PANTOPRAZOLE SODIUM SESQUIHYDRATE) Tablets and Granules

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC 20 mg enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SOMAC 40 mg enteric coated tablets, each tablet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

SOMAC 40 mg enteric coated granules, each sachet contains 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

20 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

40 mg enteric coated tablets are yellow and oval shaped, marked with the letter "P40" on one side.

40 mg granules are pale yellowish to dark brownish in colour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Gastro-oesophageal reflux disease (GORD)
 - o Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
 - o Reflux oesophagitis
 - Gastrointestinal lesions refractory to H₂ blockers
 - Zollinger-Ellison Syndrome

Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:

- Clarithromycin and amoxicillin or
- Clarithromycin and metronidazole or
- Amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism (see section 4.2 Dose and Method of Administration).

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

Children aged from 5 to 17 years

Gastro-oesophageal reflux disease (GORD)

- Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
- Reflux oesophagitis

The treatment duration should not exceed 8 weeks.

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC tablets should not be chewed or crushed but swallowed whole with a little water. SOMAC 40 mg granules should not be chewed or crushed and are intended for patients who have difficulty swallowing tablets. The granules should be sprinkled in a small volume of apple juice, orange juice or water and swallowed or administered via a nasogastric tube immediately (see 'SOMAC 40 mg Granules - Instructions for use'). The granules should be taken on an empty stomach, at least half an hour before a meal.

In *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved. One of the following combinations of pantoprazole with antibiotics is effective:

- a) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus clarithromycin 500 mg twice daily
- b) SOMAC 40 mg twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
plus clarithromycin 500 mg twice daily
- c) SOMAC 40 mg twice daily
plus amoxicillin 1000 mg (2 x 500 mg) twice daily
plus metronidazole 400 mg in the morning and 600 mg at night
- d) SOMAC 40 mg twice daily
plus bismuth subcitrate 108 mg four times a day
plus metronidazole 200 mg three times a day and 400 mg at night
plus tetracycline 500 mg (2 x 250 mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second dose of SOMAC 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SOMAC is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

In *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H₂-Receptor Antagonists. SOMAC 40 mg (1 tablet / 1 sachet of 40 mg granules) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome. The number of SOMAC 40 mg tablets/sachets of 40 mg granules should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

GORD

Symptomatic GORD (Treatment of symptomatic reflux): The recommended dosage is one SOMAC 20 mg tablet per day for adults and for children aged over 5 years. If symptom control has not been achieved after four weeks treatment with SOMAC 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day. In children over 5 years of age, the dosage should be adjusted according to weight: SOMAC 20 mg (for children 19-35 kg) or SOMAC 40 mg (for children > 35 kg) per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day in adults.

Treatment duration in children with symptomatic GORD or reflux oesophagitis should not exceed 8 weeks.

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. For long-term management, a maintenance dose of one SOMAC 20 mg or 40 mg tablet or one sachet of SOMAC 40 mg granules per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: The recommended oral dosage is one SOMAC 20 mg tablet per day.

Use in children

There is insufficient experience in children under 5 to justify a general recommendation.

Use in the elderly

The usual daily dose of 20 mg or 40 mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40 mg twice daily for a 1-week treatment period.

Impaired Renal Function

The usual daily dose of 20 mg or 40 mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

Impaired Hepatic Function

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see section 4.3 Contraindications).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

SOMAC 40 mg Granules - Instructions for use

Oral administration in apple juice, orange juice or water

1. Open sachet
2. Sprinkle intact granules into a small dispensing cup containing a small volume of apple juice, orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used.
3. Swallow immediately.
4. To ensure complete delivery of the dose, rinse the container once or twice with apple juice, orange juice or water to remove any remaining granules and swallow immediately.

Oral administration in applesauce

1. Open sachet
2. Sprinkle intact granules on a teaspoon of applesauce.
3. Swallow within 10 minutes of preparation.

Administration through nasogastric or gastric tube

For patients who have a nasogastric or gastric tube in place, SOMAC 40 mg granules can be administered as follows:

1. Separate the plunger from the barrel of a 60 mL catheter tip syringe.
2. Connect the catheter tip of the syringe to a nasogastric or gastric tube.
3. Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
4. Empty the contents of the sachet into the barrel of the syringe.
5. Add 5 mL of apple juice, pulp-free orange juice, or water and gently tap and/or shake the barrel of the syringe to help empty the syringe.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Combination therapy for eradication of *H pylori* is contraindicated in patients with known hypersensitivity to any of the antibiotics proposed for combination therapy for eradication of *H pylori* or in patients with moderate to severe hepatic or renal dysfunction. The product information for the individual components of the combination *H pylori* eradication therapy should be consulted for any further contraindications.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see section 4.5 Interactions with Other Medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check the following before use

In the case of combination therapy for the eradication of *H pylori*, the product information for the antibiotics used in the combination should be observed.

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Clostridium difficile

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption (such as the elderly) on long-term therapy and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment or if respective clinical symptoms are observed. Rare cases of cyanocobalamin (vitamin B₁₂) deficiency following acid-blocking therapy have been reported.

Non-steroidal anti-inflammatory drugs

Use of SOMAC 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (see section 4.8 Adverse Effects (Undesirable Effects)). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; with estimated exposures at these doses at, or below, the clinical exposure, all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (with exposures (AUC) of 0.2- to 10-fold (oral) and 1- to 2-fold (IV) the clinical exposure). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses up to 15 mg/kg/day (up to 7- to 9-fold the clinical exposure of the 40 mg IV dose) for 4 weeks.

Monitoring

In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with SOMAC 20 mg who do not respond after 4 weeks should be investigated.

Use in the elderly

No dose adjustment is necessary in elderly patients (see Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4. Special Warnings and Precautions For Use; Influence on vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; Special populations).

Paediatric use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be

co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced foetal weight at 150 mg/kg/day or greater (AUC exposure approximately 18-fold clinical exposure) and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day (approximately clinical exposure). For the latter a no-effect dose of 5 mg/kg was established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SOMAC tablets and granules are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in combination with antibiotics for *H pylori* eradication in clinical trials and post-marketing surveillance.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$; not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: Fatigue and malaise, asthenia and increased sweating

Rare: fever, peripheral oedema and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea/ vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis, jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings Precautions for Use).

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (TIN) (with possible progression to renal failure)

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation, and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash/ exanthema/ eruption

Rare: angioedema, urticaria

Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis

Eye disorders

Uncommon: visual disturbances (blurred vision)

Very rare: conjunctivitis

Table 1 Incidence (%) of Common (>1%) and Uncommon (<1%) Adverse Events in Clinical Trials of Triple Therapy containing pantoprazole in combination with two antibiotics for *H pylori* eradication

Event	PCM/T* n=725	PAC n=492	PAM n=146
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

*T = tinidazole, used in place of metronidazole in one clinical study

Table 2 Adverse events ($\geq 1\%$) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

Adverse event	PBMT (n=422)	BMT (n=600)	PAC (n= 368)
Skin & appendages disorders			
Rash	7 (1.7%)	16 (2.7%)	4 (1.1%)
Pruritus ani	---	7 (1.2%)	---
Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders			
Moniliasis	6 (1.4%)	---	5 (1.4%)

---- Events reported by $< 1\%$

The following safety data for patients aged 2 to 16 years (n = 250) is collated from 5 clinical studies (3001A1-109-US, 3001K1-110-US, 3001A1-322-US, 3001A1-326-US and BYK1023/MEX008).

	Overall Children		
Patients (N)	250		
	No of AE	No of patients with AE	% patients with AE
Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v. or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

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

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. The effect of pantoprazole sodium oral formulations (tablets and granules) and the intravenous formulation on gastric acidity is comparable.

Clinical trials In Adults

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see section 4.2 Dose And Method Of Administration). In an experimental study in mice, pantoprazole at a dose of 100 mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Eradication of *H pylori*

The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 3 Clinical trials comparing triple therapies containing pantoprazole in combination with two antibiotics

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxycillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		----- PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8%
		----- PAC 80/2000/1000	14/14/14	34		91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0%
		----- PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8) GU (3) HU (6) FD (13)	80.0 %
VMG402	Double Blind Randomised	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %

Study BY1023	Design	Therapy Scheme (mg per day)	Days of medication	N (MITT)	Indication (N)	Eradication rate (MITT)
		----- PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomised	PAC-P 80/2000/1000-40 ----- PCM-P 80/1000/1000-40	See results for PAC regime above			
FK3049	Open Randomised	PCM-P 80/1500/1500-40 -----	7/7/7/-21	136	DU (277)	89.0 %
		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxycillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24) GU (24)	81.3%
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5%
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6) HU (13) FD (11)	70.0%

Table 4 A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	N (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P	pantoprazole	DU	duodenal ulcer
PAC	pantoprazole/amoxicillin/clarithromycin	GU	gastric ulcer
PCM	pantoprazole/clarithromycin/metronidazole	HU	history of ulcer
PAM	pantoprazole/amoxicillin/metronidazole	HDU	history of duodenal ulcer
PBMT	pantoprazole/bismuth/metronidazole/tetracycline	NUD	non ulcer dyspepsia
BMT	bismuth/metronidazole/tetracycline	FD	functional dyspepsia
PC	pantoprazole/clarithromycin	GAS	gastritis
MITT	modified intention to treat	ERO	erosions

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 5.

Table 5 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux.

	1 week			2 weeks		
Data Set	SOMAC 20	Placebo	P	SOMAC 20	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis

In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after 4 and 8 weeks is shown in Table 6. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 6 Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat).

Trial/Group	N	% Patients Healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		P < 0.05	P < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		P < 0.05	P < 0.05

Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis

Three randomised, double-blind, parallel-group trials examined the efficacy of pantoprazole in the maintenance of healed reflux oesophagitis in patients aged 18-88 years treated for moderate to severe reflux oesophagitis over 12 months. The primary endpoint was time to endoscopically-confirmed relapse; however, the median was not reached in the pantoprazole groups at the end of 12 months. Table 7 lists the results for the incidence of relapse, in patients with data from at least one follow-up visit.

Table 7 Incidence of relapse 1 (%) of reflux oesophagitis 2 in controlled trials of 12 months duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/d	Pantoprazole 40 mg/d	Ranitidine 150 mg/d	Difference [90% CI]
FK3028	25% (n=221)	22% (n=212)	-	2.7% [-5,10]
FK3033	28% (n=203)	19% (n=193)	-	9% [1, 17]
BGSA008	35% (n=75)	-	72% (n=40)	37% [23,52]

1 Endoscopically confirmed

2 Patients were enrolled in the study with Savary-Miller stage 2-3 reflux oesophagitis. Patients were initially healed of their reflux oesophagitis with a short term treatment of up to 8 weeks with either pantoprazole or omeprazole. Following healing of reflux oesophagitis, patients were then enrolled in the long-term prevention study for up to 12 months. Relapse was defined as endoscopically confirmed presence of reflux oesophagitis.

Pantoprazole 20 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within $\pm 20\%$.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients

experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Additionally, in the open on-going studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment

Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the “therapeutic failure” rate after 6 months, defined as “endoscopic failure” (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least “likely” related adverse event or due to severe gastrointestinal symptoms.

Study 205/2000

A total of 515 patients were included in the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=257) or misoprostol 200 µg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

Table 8 Results, Efficacy

	Time interval (months)	Pantoprazole	Misoprostol	
Total number of patients		257	258	
“In Remission” with regard to:		[%]	[%]	p-value
Therapeutic failure	0 – 6	89.3	70.3	< 0.001
Endoscopic failure	0 – 6	94.7	85.7	0.005
Symptomatic failure	0 – 6	98.5	91.7	0.002

Pantoprazole 20 mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to “therapeutic failure” and to “endoscopic failure”. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n=196), pantoprazole 40 mg daily (n=199) or omeprazole 20 mg daily (n=200). Efficacy results are shown in the table below.

Table 9 Results, Efficacy

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total number of patients		196	199	200
“In Remission” with regard to:		[%]	[%]	[%]
Therapeutic failure	0 – 6	89.8	93.1	88.7
Endoscopic failure	0 – 6	91.4	95.3	93.3
Symptomatic failure	0 – 6	98.1	100	98.1

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

Study 3001B1-332-US (211/2006)

In a study in patients with gastro-oesophageal reflux disease and a history of erosive oesophagitis, pantoprazole 40 mg granules were comparable to pantoprazole 40 mg tablets with regard to maximum acid output and pH parameters (e.g. mean and median percentage of time with intragastric pH > 4, and median intragastric pH).

Clinical Trials in Children

In 2 studies pantoprazole 20 mg or 40 mg daily was given to 189 children aged from 5 to 16 years with symptomatic GORD. A similar reduction in symptoms of GORD was reported with both doses in both studies.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Adults

After administration of enteric-coated tablets, pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL following a 20 mg dose. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. In a comparative bioavailability study, an investigational formulation of pantoprazole 40 mg granules showed similar oral bioavailability (AUC) relative to the pantoprazole 40 mg tablets. The investigational formulation of pantoprazole 40 mg granules was shown to be bioequivalent to the marketed granules formulation. The rate of absorption (C_{max}) was reduced with the investigational granules as compared to the tablet. The absolute bioavailability of the tablet is approximately 77%. C_{max} of pantoprazole 40 mg granules is 1.9 mg/L and is reached after about 2-2.5 hours under fasting conditions. The AUC is approximately 4.0 mg.h/L. Concomitant intake of food had no influence on the AUC and C_{max} of the pantoprazole 40 mg tablet and thus its bioavailability. However, for the investigational formulation of pantoprazole 40 mg granules this resulted in a reduction of the AUC (30%), C_{max} (50%) and a delay in T_{max} . This influence of food was reduced if the investigational formulation of granules were administered 30 minutes before the intake of food.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is extensively metabolised in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolisers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (523%) with once daily dosing.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

Special populations

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Children

Following administration of single oral doses of 20 mg or 40 mg of pantoprazole to children aged 5-16 years, AUC and C_{max} were in the same range as the corresponding values observed in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg of pantoprazole to children aged 2-16 years AUC and volume of distribution were in accordance with data from adults and there was no significant association between pantoprazole clearance and age or weight.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected

clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. This is an estimated exposure 24-fold the clinical exposure from the 40 mg tablet. No distinct DNA-adduct was detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7- to 100- and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity

In a two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The estimated exposure (based on AUC) from these doses is at, or below, clinical exposure from a 40 mg tablet. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day, with respective estimated exposures of 1- and 9-fold the AUC of the 40 mg clinical dose. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (exposure similar to clinical exposure), may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day (exposure approximately 9-fold clinical exposure) also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower oral doses (5, 15 and 50 mg/kg/day, 0.5-, 2- and 7-fold the clinical AUC, respectively). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males, while none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains; sodium carbonate, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

Each unit dose sachet of granules also contains; microcrystalline cellulose, sodium carbonate, crospovidone, EUDRAGIT L30D-55, hypromellose, polysorbate 80, povidone, titanium dioxide, iron oxide yellow, triethyl citrate, and purified talc.

6.2 INCOMPATIBILITIES

Not applicable, please refer to Section 4.5-Interactions with other medicines and other forms of interactions.

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

SOMAC tablets in blister packs: Store below 30°C.

SOMAC 40 mg granules in sachets: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg and 40 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 5s, 14s, 15s, 28s, 30s, 50s, 56s, 60s, 100s, 140s and

40 mg granules are available in:

- Plastic laminate/aluminium single dose sachets in packs of 5s, 28s, 30s and 84s.

Not all presentations and pack sizes are being distributed in Australia.

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

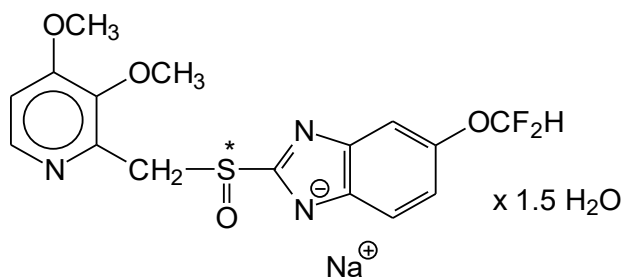
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

Molecular weight: 432.4 (sodium salt x 1.5 H₂O)

Structural formula:



CAS number

164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
 Level 39
 225 George Street
 Sydney NSW 2000
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 Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

17 July 2025

Summary table of changes

Section changed	Summary of new information
6.4 & 6.5	Removal of bottle presentation

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Consumer Medicine Information (CMI) summary

The [full CMI](#) on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using SOMAC?

SOMAC contains the active ingredient pantoprazole sodium sesquihydrate. SOMAC is used to treat and help heal duodenal and gastric ulcers. SOMAC may also be used to prevent ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). SOMAC is also used to treat reflux oesophagitis or reflux disease and can be used to prevent reflux oesophagitis from coming back. SOMAC is also used to treat a rare condition called Zollinger-Ellison syndrome.

For more information, see Section [1. Why am I using SOMAC?](#) in the full CMI.

2. What should I know before I use SOMAC?

Do not use if you have ever had an allergic reaction to pantoprazole or any of the ingredients listed at the end of the CMI. **Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding. Tell your doctor if you have severe liver disease or cirrhosis.**

For more information, see Section [2. What should I know before I use SOMAC?](#) in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with SOMAC and affect how it works. A list of these medicines is in Section [3. What if I am taking other medicines?](#) in the full CMI.

4. How do I use SOMAC?

The dose of SOMAC that your doctor prescribes for you depends on your medical condition. Take Somac for as long as your doctor instructs you to. Swallow SOMAC tablets whole with a little water with or without food. Do not crush or chew the tablets. Take SOMAC granules half an hour before a meal without chewing or crushing the granules. Take the granules in apple juice, orange juice or water. More instructions can be found in Section [4. How do I use SOMAC?](#) in the full CMI.

5. What should I know while using SOMAC?

Things you should do	- Remind any doctor, dentist or pharmacist you visit that you are using SOMAC. - Tell your doctor if you are pregnant or plan to become pregnant or are breastfeeding.
Things you should not do	- Do not stop using SOMAC without talking to your doctor first. - Do not use SOMAC to treat any other complaints unless your doctor tells you to. - Do not give SOMAC to anyone else, even if they have the same symptoms as you.
Driving or using machines	Do not drive or operate machinery if SOMAC affects your ability to concentrate and react.
Drinking alcohol	Your doctor may advise you to limit your alcohol intake to help your condition.
Looking after your medicine	Keep SOMAC in a cool, dry place where the temperature stays below 25°C (granules) or 30°C (tablets).

For more information, see Section [5. What should I know while using SOMAC?](#) in the full CMI.

6. Are there any side effects?

Headache, dizziness, diarrhoea, nausea or vomiting, stomach pain, excessive gas in stomach or bowel, indigestion, constipation, sore breasts, dry mouth, taste disturbances, metallic taste, weakness/ tiredness, trouble sleeping. Increased sweating/body temperature, blurred vision, skin problems, unusual tiredness or weakness, tingling or numbness, blood in urine, increased or decreased need to urinate, frequent infections, chest pain, high blood pressure, irregular heartbeat, water retention, swelling, bleeding/bruising more easily than normal, depression, confusion or anxiety, bone fracture of hip, wrist or spine, seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps, severe and/or persistent diarrhoea. Signs of liver inflammation including yellowing of skin/eyes, nausea, vomiting, loss of appetite, feeling unwell, fever, itching and dark coloured urine; severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of skin or rash when exposed to sun, possibly with pain in joints and general fever; swelling of face, lips, mouth, tongue or throat which may cause difficulty swallowing or breathing; shortness of breath, wheezing or difficulty breathing; black stools; vomiting blood.

For more information, including what to do if you have any side effects, see Section [6. Are there any side effects?](#) in the full CMI.

Somac[®] Tablets and Granules

Active ingredient(s): *pantoprazole sodium sesquihydrate*

Consumer Medicine Information (CMI)

This leaflet provides important information about using SOMAC. It does not take the place of talking to your doctor or pharmacist. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using SOMAC.**

Where to find information in this leaflet:

1. [Why am I using SOMAC?](#)
2. [What should I know before I use SOMAC?](#)
3. [What if I am taking other medicines?](#)
4. [How do I use SOMAC?](#)
5. [What should I know while using SOMAC?](#)
6. [Are there any side effects?](#)
7. [Product details](#)

1. Why am I using SOMAC?

SOMAC contains the active ingredient pantoprazole sodium sesquihydrate. SOMAC belongs to a group of medicines called proton pump inhibitors (PPIs). SOMAC works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place.

Ulcers

SOMAC is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

Most people who have a peptic ulcer also have bacteria called *Helicobacter pylori* in their stomach. When SOMAC is taken with antibiotics the combination therapy will kill the *Helicobacter pylori* and let your ulcer heal.

SOMAC may also be used to prevent ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). These are medicines used to relieve pain, swelling and other symptoms of inflammation, including arthritis (inflammation of the joints).

Reflux disease

SOMAC is also used to treat reflux oesophagitis or reflux disease. This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

SOMAC is also used to prevent reflux oesophagitis from coming back.

Zollinger-Ellison syndrome

SOMAC is also used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

2. What should I know before I use SOMAC?

Warnings

Do not use SOMAC if:

- you are allergic to pantoprazole sodium sesquihydrate, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicines containing proton pump inhibitors.
- always check the ingredients to make sure you can use this medicine.
- symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, rash, itching or hives on the skin.
- you have severe liver disease or cirrhosis.
- after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering. If it has expired or is damaged return it to your pharmacist for disposal.

Do not take SOMAC in combination with antibiotics or any other medicine if:

- you are allergic to any of the antibiotics or medicines your doctor may prescribe with SOMAC
- you have moderate to severe liver or kidney disease

Do not take SOMAC in combination with atazanavir or nelfinavir (anti-viral medications).

Do not give SOMAC to children under 5 years of age.

There is not enough information to recommend the use of this medicine for children under the age of 5 years.

Check with your doctor if you:

- you have any allergies to any other medicines, foods, preservatives or dyes
- have reduced body stores or risk factors for reduced vitamin B12, as pantoprazole may lead to a reduced absorption of vitamin B12
- have any other medical conditions
- take any medicines for any other condition

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss

- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take SOMAC.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section [6. Are there any side effects?](#)

Pregnancy and breastfeeding

Check with your doctor if you are pregnant or intend to become pregnant. It is not known if it is safe for you to take SOMAC while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed. It is not known if your baby can take in SOMAC from breast milk if you are breastfeeding.

Ask your doctor about the risks and benefits involved.

3. What if I am taking other medicines?

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

Do not take SOMAC in combination with atazanavir or nelfinavir (anti-viral medications).

Some medicines and SOMAC may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by SOMAC or may affect how well it works. You may need to use different amounts of your medicine or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful with or to avoid while taking SOMAC.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect SOMAC.

4. How do I use SOMAC?

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, ask your doctor or pharmacist for help.

How much to take

The dose and frequency of SOMAC that your doctor prescribes for you depends on your medical condition.

Your doctor may change the dose as your condition changes.

The usual dose is 20 or 40 mg per day.

However, if your doctor also prescribes antibiotics in combination with SOMAC for the treatment of duodenal ulcers, the dose of SOMAC is 80 mg per day. The first 40 mg dose should be taken in the morning and the second should be taken before the evening meal for 7 days.

Your doctor will prescribe the dose that is right for you.

In children over 5 years of age, the dose of SOMAC for reflux oesophagitis or reflux disease is based on weight and may be 20 mg or 40 mg per day, depending on the condition being treated.

Take Somac for as long as your doctor instructs you to.

When to take SOMAC

SOMAC should be taken around the same time each day.

Taking it at the same time each day will have the best effect. It will also help you remember when to take it.

If you are taking other medicines, like antibiotics, in combination with SOMAC therapy, follow the instructions for the use of each medicine carefully.

How to take SOMAC

Tablets:

Swallow your tablets whole with a little water with or without food.

Do not crush or chew the tablets. SOMAC tablets have a special coating to protect them from the acidic contents of your stomach. For SOMAC to work effectively, this coating must not be broken.

Granules:

If you are using SOMAC granules, take it half an hour before a meal without chewing or crushing the granules.

Take the granules in apple juice, orange juice or water as follows:

1. open sachet
2. sprinkle intact granules into a small volume of apple juice, pulp-free orange juice, or water (at least 15 mL). Alternatively, a tablespoon may be used
3. mix briefly just before drinking
4. drink straight away

5. to ensure that you have taken all the medicine, rinse the container thoroughly once or twice with apple juice, orange juice or water to remove any remaining granules and drink immediately

You can also take the granules in apple sauce as follows:

1. open sachet
2. sprinkle intact granules on a teaspoon of apple sauce
3. swallow within 10 minutes of preparation

Do not crush or chew the granules. SOMAC granules have a special coating to protect them from the acidic contents of your stomach. For SOMAC to work effectively, this coating must not be broken.

SOMAC granules are intended for people who have difficulty swallowing tablets including those who require a nasogastric tube.

If you forget to take SOMAC

SOMAC should be used regularly at the same time each day.

If you miss your dose at the usual time, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose you missed. This may increase the chance of getting an unwanted side effect.

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

If you use too much SOMAC

If you think that you have used too much SOMAC, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (**by calling 13 11 26**), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using SOMAC?

Things you should do

- If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking SOMAC.
- Tell any other doctors, dentists and pharmacists who treat you that you are taking SOMAC.
- If you are going to have surgery, tell the surgeon that you are taking SOMAC.
- If you become pregnant while you are taking SOMAC, tell your doctor or pharmacist immediately.

- **If you are about to have any blood tests, tell your doctor that you are taking SOMAC.** It may interfere with the results of some tests.
- **Keep all of your doctor's appointments so that your progress can be checked.** Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.
- **Tell your doctor if your reflux symptoms return after you stop taking this medicine.** The symptoms of reflux may return after stopping this medicine suddenly, especially if you have taken it for a while.

Things you should not do

- Do not use SOMAC to treat any other complaints unless your doctor tells you to.
- Do not give SOMAC to anyone else, even if they have the same symptoms as you.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how SOMAC affects you. A small number of patients have felt dizzy or had problems with their vision after taking SOMAC.

Things that may help your condition

Some self-help measures suggested below may help your condition. Your doctor or pharmacist can give you more information about these measures.

- **Alcohol** – your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, 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 which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** – eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **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.

Looking after your medicine

- Keep your tablets in their blister, and granules in their sachet pack until it is time to take them.
- Follow the instructions on the carton on how to take care of your medicine properly.
- Keep SOMAC in a cool, dry place where the temperature stays below 25°C (granules) or 30°C (tablets).

- Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car. 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.

When to discard your medicine

If your doctor tells you to stop taking this medicine or if the medicines have passed their expiry date, ask your pharmacist what to do with any tablets or granules that are left over.

Getting rid of any unwanted medicine

If you no longer need to take this medicine or it is out of date, take it to any pharmacy for safe disposal.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
- headache - dizziness - diarrhoea - nausea or vomiting - stomach pain - excessive gas in the stomach or bowel - indigestion - constipation - sore breasts - dry mouth - metallic taste - taste disturbances - weakness or tiredness - trouble sleeping - increased sweating or body temperature - blurred vision - skin problems such as itchiness and rash	Speak to your doctor if you have any of these less serious side effects and they worry you.

Serious side effects

Serious side effects	What to do
- unusual tiredness or weakness - tingling or numbness ("pins and needles") - blood in the urine - increased or decreased need to urinate - frequent infections such as fever, severe chills, sore throat or mouth ulcers - chest pain - high blood pressure - irregular (fast or slow) heartbeat - water retention, swelling - bleeding or bruising more easily than normal - depression, confusion or anxiety - bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer)) - symptoms such as seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps. These can be a sign of low magnesium, calcium or potassium levels in your blood - severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea	Speak to your doctor immediately if you have any of these side effects. These side effects may require medical attention.
- signs of liver inflammation including yellowing of the skin or eyes, nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching and dark coloured urine - severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints and general fever - swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing - shortness of breath, wheezing or difficulty breathing - black (blood stained) stools - vomiting blood	Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What SOMAC contains

Active ingredient (main ingredient)	pantoprazole sodium sesquihydrate
Other ingredients (inactive ingredients)	Tablets: • sodium carbonate • mannitol • crospovidone • povidone • calcium stearate • hypromellose • titanium dioxide • iron oxide yellow • propylene glycol • methacrylic acid copolymer • polysorbate 80 • sodium lauryl sulfate • triethyl citrate • opacode brown S-1-16530 printing ink Granules: • microcrystalline cellulose • sodium carbonate • crospovidone • hypromellose • polysorbate 80 • povidone • titanium dioxide • iron oxide yellow • EUDRAGIT L30D-55 • triethyl citrate • purified talc

Do not take this medicine if you are allergic to any of these ingredients.

Somac tablets and granules do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

What SOMAC looks like

Tablets:

SOMAC 20 mg tablets - yellow and oval shaped, marked with 'P20' on one side. SOMAC 20 mg tablets are available in blister packs of 30 tablets. (AUST R 70829)

SOMAC 40 mg tablets - yellow and oval shaped, marked with 'P40' on one side. SOMAC 40 mg tablets are available in blister packs of 30 tablets. (AUST R 69792)

Granules:

SOMAC 40 mg granules – pale yellowish to dark brownish in colour. SOMAC 40 mg granules are available in single aluminium foil sachets in packs of 30 sachets. (AUST R 148005)

Who distributes SOMAC

Takeda Pharmaceuticals Australia Pty Ltd

Level 39

225 George Street

Sydney NSW 2000

Australia

Telephone: 1800 012 612

www.takeda.com/en-au

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Consumer Medicine Information (CMI) summary

The [full CMI](#) on the next page has more details. If you are worried about using this medicine, speak to your doctor or pharmacist.

1. Why am I using SOMAC Injection?

SOMAC Injection contains the active ingredient pantoprazole sodium. SOMAC Injection is used to treat and help heal duodenal and gastric ulcers. SOMAC Injection is also used to treat reflux oesophagitis or reflux disease and can be used to prevent reflux oesophagitis from coming back. SOMAC Injection is also used to treat a rare condition called Zollinger-Ellison syndrome. For more information, see Section [1. Why am I using SOMAC injection?](#) in the full CMI.

2. What should I know before I use SOMAC Injection?

Do not use if you have ever had an allergic reaction to pantoprazole or any of the ingredients listed at the end of the CMI. **Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding. Tell your doctor if you have severe liver disease or cirrhosis.**

For more information, see Section [2. What should I know before I use SOMAC Injection?](#) in the full CMI.

3. What if I am taking other medicines?

Some medicines may interfere with SOMAC Injection and affect how it works.

A list of these medicines is in Section [3. What if I am taking other medicines?](#) in the full CMI.

4. How do I use SOMAC Injection?

The dose and frequency of SOMAC Injection that your doctor prescribes for you depends on your medical condition. Your doctor may change the dose as your condition changes. Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist. More instructions can be found in Section [4. How do I use SOMAC Injection?](#) in the full CMI.

5. What should I know while using SOMAC Injection?

Things you should do	- Remind any doctor, dentist or pharmacist you visit that you are using SOMAC Injection. - Tell your doctor if you are pregnant or plan to become pregnant or are breastfeeding.
Things you should not do	- Do not stop using SOMAC Injection without talking to your doctor first. - Do not use SOMAC Injection to treat any other complaints unless your doctor tells you to. - Do not give SOMAC Injection to anyone else, even if they have the same symptoms as you.
Driving or using machines	Do not drive or operate machinery if SOMAC Injection affects your ability to concentrate and react.
Drinking alcohol	Your doctor may advise you to limit your alcohol intake to help your condition.
Looking after your medicine	Keep SOMAC Injection in a cool place where the temperature stays below 25°C. Keep the vial in the outer carton to protect from light.

For more information, see Section [5. What should I know while using SOMAC Injection?](#) in the full CMI.

6. Are there any side effects?

Headache, dizziness, diarrhoea, nausea or vomiting, stomach pain, excessive gas in stomach or bowel, indigestion, constipation, sore breasts, dry mouth, taste disturbances, metallic taste, weakness/ tiredness, trouble sleeping, pain and swelling at the site of injection, increased sweating/body temperature, blurred vision, skin problems, unusual tiredness or weakness, tingling or numbness, blood in urine, increased or decreased need to urinate, frequent infections, chest pain, high blood pressure, irregular heartbeat, water retention, swelling, bleeding/bruising more easily than normal, depression, confusion or anxiety, bone fracture of hip, wrist or spine, seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps, severe and/or persistent diarrhoea. Signs of liver inflammation including yellowing of skin/eyes, nausea, vomiting, loss of appetite, feeling unwell, fever, itching and dark coloured urine; severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of skin or rash when exposed to sun, possibly with pain in joints and general fever; swelling of face, lips, mouth, tongue or throat which may cause difficulty swallowing or breathing; shortness of breath, wheezing or difficulty breathing; black stools; vomiting blood.

For more information, including what to do if you have any side effects, see Section [6. Are there any side effects?](#) in the full CMI.

Somac[®] Injection

Active ingredient(s): *pantoprazole sodium*

FOI 26-2973 - Document 37

Consumer Medicine Information (CMI)

This leaflet provides important information about using SOMAC Injection. It does not take the place of talking to your doctor or pharmacist. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using SOMAC Injection.**

Where to find information in this leaflet:

1. [Why am I using SOMAC Injection?](#)
2. [What should I know before I use SOMAC Injection?](#)
3. [What if I am taking other medicines Injection?](#)
4. [How do I use SOMAC Injection?](#)
5. [What should I know while using SOMAC Injection?](#)
6. [Are there any side effects?](#)
7. [Product details](#)

1. Why am I using SOMAC Injection?

SOMAC Injection contains the active ingredient pantoprazole sodium. SOMAC Injection belongs to a group of medicines called proton pump inhibitors (PPIs). SOMAC Injection works by decreasing the amount of acid the stomach makes, to give relief from the symptoms and allow healing to take place.

Ulcers

SOMAC Injection is used to treat and help heal duodenal and gastric ulcers.

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.

These can be caused in part by too much acid being made in the stomach.

Reflux disease

SOMAC Injection is also used to treat reflux oesophagitis or reflux disease. This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

SOMAC Injection is also used to prevent reflux oesophagitis from coming back.

Zollinger-Ellison syndrome

SOMAC Injection is also used to treat a rare condition called Zollinger-Ellison syndrome, where the stomach produces very large amounts of acid, much more than in ulcers and reflux disease.

2. What should I know before I use SOMAC Injection?

Warnings

Do not take SOMAC Injection if:

- you are allergic to pantoprazole sodium, or any of the ingredients listed at the end of this leaflet.
- you are allergic to any medicines containing proton pump inhibitors.
- always check the ingredients to make sure you can use this medicine.
- symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, rash, itching or hives on the skin.
- you have severe liver disease or cirrhosis.
- after the expiry date printed on the pack or if the packaging is damaged or shows signs of tampering. If it has expired or is damaged return it to your pharmacist for disposal.

Do not take SOMAC Injection in combination with atazanavir or nelfinavir (anti-viral medications).

Do not give SOMAC Injection to children under 5 years of age. There is not enough information to recommend the use of this medicine for children under the age of 5 years.

Check with your doctor if you:

- you have any allergies to any other medicines, foods, preservatives or dyes
- have reduced body stores or risk factors for reduced vitamin B12, as pantoprazole may lead to a reduced absorption of vitamin B12
- have any other medical conditions
- take any medicines for any other condition

Tell your doctor if you have any of the following symptoms:

- unintentional weight loss
- repeated vomiting
- vomiting blood
- difficulty or pain when swallowing
- you look pale and feel weak
- you notice blood in your stools

Your doctor may need to perform some additional tests before you take SOMAC Injection.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section [6. Are there any side effects?](#)

Pregnancy and breastfeeding

Check with your doctor if you are pregnant or intend to become pregnant. It is not known if it is safe for you to take SOMAC Injection while you are pregnant. It may affect your baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed. It is not known if your baby can take in SOMAC Injection from breast milk if you are breastfeeding.

Ask your doctor about the risks and benefits involved.

3. What if I am taking other medicines?

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

Do not take SOMAC Injection in combination with atazanavir or nelfinavir (anti-viral medications).

Some medicines and SOMAC Injection may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (anticoagulants)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by SOMAC Injection or may affect how well it works. You may need to use different amounts of your medicine or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful with or to avoid while taking SOMAC Injection.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect SOMAC Injection.

4. How do I use SOMAC Injection?

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, ask your doctor or pharmacist for help.

How much to take

The dose and frequency of SOMAC Injection that your doctor prescribes for you depends on your medical condition.

Your doctor may change the dose as your condition changes.

When to take SOMAC Injection

Your doctor will determine when you are to be given Somac Injection.

How to take SOMAC Injection

Somac Injection is reconstituted with sodium chloride solution by your doctor or pharmacist.

Your doctor will determine how long you need to be treated with Somac Injection.

SOMAC Injection is intended for people who are unable to take tablets or granules.

If you forget to take SOMAC Injection

SOMAC Injection should be used regularly at the same time each day.

If a dose of Somac Injection is missed, your doctor will determine when your next dose is due.

If you take too much SOMAC Injection

If you think that you have been given too much SOMAC Injection, you may need urgent medical attention.

You should immediately:

- phone the Poisons Information Centre (by calling 13 11 26), or
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using SOMAC Injection?

Things you should do

- **If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking SOMAC Injection.**
- **Tell any other doctors, dentists and pharmacists who treat you that you are taking SOMAC Injection.**
- **If you are going to have surgery, tell the surgeon that you are taking SOMAC Injection.**
- **If you become pregnant while you are taking SOMAC Injection, tell your doctor or pharmacist immediately.**
- **If you are about to have any blood tests, tell your doctor that you are taking SOMAC Injection.** It may interfere with the results of some tests.
- **Keep all of your doctor's appointments so that your progress can be checked.** Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.
- **Tell your doctor if your reflux symptoms return after you stop taking this medicine.** The symptoms of reflux may return after stopping this medicine suddenly, especially if you have taken it for a while.

Things you should not do

- Do not use SOMAC Injection to treat any other complaints unless your doctor tells you to.
- Do not give SOMAC Injection to anyone else, even if they have the same symptoms as you.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how SOMAC Injection affects you. A small number of patients have felt dizzy or had problems with their vision after taking SOMAC.

Things that may help your condition

Some self-help measures suggested below may help your condition. Your doctor or pharmacist can give you more information about these measures.

- **Alcohol** – your doctor may advise you to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, 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 which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** – eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **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.

Looking after your medicine

- Normally your doctor will provide your Somac Injection. If however, you do take your Somac Injection from the pharmacy to your doctor, it is important to keep SOMAC Injection in a cool place where the temperature stays below 25°C. Keep the vial in the outer carton to protect from light.
- Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car. 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.

If for any reason you take your Somac Injection home, use as soon as possible after preparation. If storage is necessary, store at 2-8°C for no longer than 12 hours.

When to discard your medicine

If your doctor stops treating you with Somac Injection, your hospital pharmacist will dispose of any unused medicine.

Do not use this medicine after the expiry date.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

Less serious side effects	What to do
• headache • dizziness • diarrhoea • nausea or vomiting • stomach pain • excessive gas in the stomach or bowel • indigestion • constipation • sore breasts • dry mouth • metallic taste • taste disturbances • weakness or tiredness • trouble sleeping • pain and swelling at the site of injection • increased sweating or body temperature • blurred vision • skin problems such as itchiness and rash	Speak to your doctor if you have any of these less serious side effects and they worry you.

Serious side effects

Serious side effects	What to do
• unusual tiredness or weakness • tingling or numbness ("pins and needles") • blood in the urine • increased or decreased need to urinate • frequent infections such as fever, severe chills, sore throat or mouth ulcers • chest pain • high blood pressure • irregular (fast or slow) heartbeat • water retention, swelling	Speak to your doctor immediately if you have any of these side effects. These side effects may require medical attention.

Serious side effects	What to do
- bleeding or bruising more easily than normal - depression, confusion or anxiety - bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer)) - symptoms such as seizures, abnormal or fast heartbeat, jerking/shaking movements or muscle cramps. These can be a sign of low magnesium, calcium or potassium levels in your blood - severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea	
- signs of liver inflammation including yellowing of the skin or eyes, nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching and dark coloured urine - severe skin problems such as itchiness, redness, rash with swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints and general fever - swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing - shortness of breath, wheezing or difficulty breathing - black (blood stained) stools vomiting blood	Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects

After you have received medical advice for any side effects you experience, you can report side effects to the Therapeutic Goods Administration online at www.tga.gov.au/reporting-problems. By reporting side effects, you can help provide more information on the safety of this medicine.

Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What SOMAC Injection contains

Active ingredient (main ingredient)	pantoprazole sodium
Other ingredients (inactive ingredients)	- disodium edetate - sodium hydroxide

Do not take this medicine if you are allergic to any of these ingredients.

Somac Injection does not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

What SOMAC Injection looks like

Somac Injection is available as 40 mg injection. Somac Injection is a white to off-white powder provided in a glass vial.

Australian Registration Number

AUST R 121427

Who distributes SOMAC Injection

Takeda Pharmaceuticals Australia Pty Ltd

Level 39

225 George Street

Sydney NSW 2000

Australia

Telephone: 1800 012 612

www.takeda.com/en-au

This leaflet was prepared in July 2025.

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AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] HEARTBURN RELIEF (PANTOPRAZOLE SODIUM SESQUIHYDRATE)

1 NAME OF THE MEDICINE

Pantoprazole (as pantoprazole sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC Heartburn Relief enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SOMAC Heartburn Relief enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SOMAC Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on Vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption such as the elderly and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions or if respective clinical symptoms are observed. Rare cases of cyanocobalamin deficiency following acid-blocking therapy have been reported.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. 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

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

See Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4 Special Warnings and Precautions For Use; Influence on Vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; special populations.

Paediatric use

To date there has been limited experience with treatment in children.

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.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see Section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as

dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listed in descending order of frequency

(Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$, not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating

Rare: fever, peripheral oedema, and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: flatulence, severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes
 Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings and Precautions for Use)).

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia
 Very rare: pain including skeletal pain
 Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: tubulointerstitial nephritis (TIN) (with possible progression to renal failure)

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis
 Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Psychiatric disorders

Uncommon: sleep disorders
 Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence
 Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption
 Rare: angioedema and urticaria
 Very rare: severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity
 Unknown: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: disturbances in vision (blurred vision)
 Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. Treatment should be symptomatic and supportive measures should be utilised. For information on the management of overdosage, contact the Poisons Information centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pantoprazole is a proton pump inhibitor (PPI). Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in [Table 1](#).

Table 1 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20 mg	Placebo	P	pantoprazole 20 mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

Special populations

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

6.2 INCOMPATIBILITIES

Please see Section 4.5 - Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

SOMAC Heartburn Relief 20 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 2s, 7s and 14s.

*Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

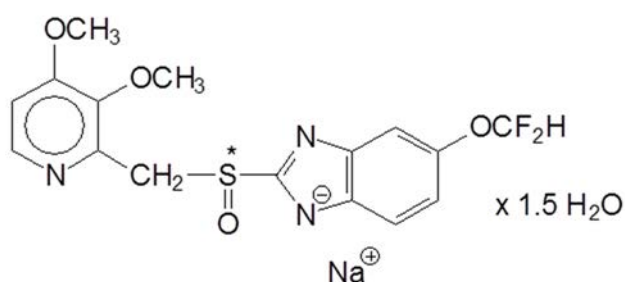
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

CAS number

Chemical name (CAS)	Sodium-[5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S.1½ H ₂ O
CAS number:	164579-32-2
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacy Only Medicine (Schedule 2) – 2* and 7 tablets

Pharmacist Only Medicine (Schedule 3) – 14 tablets

*Not all pack sizes may be marketed

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
 Level 39
 225 George Street
 Sydney NSW 2000
 Australia
 Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

Pharmacy Only Medicine (Schedule 2) – 27 February 2015

Pharmacist Only Medicine (Schedule 3) – 1 August 2008

10 DATE OF REVISION

Summary table of changes

Section changed	Summary of new information
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS.
4.8	Addition of Subacute Cutaneous Lupus Erythematosus
8	Revision of sponsor address details and addition of sponsor website
4.8	Revision of AE, tubulointerstitial nephritis

SOMAC HEARTBURN RELIEF[®] is a registered trademark of Takeda GmbH.

V03 73 x 18 x 117 mm

ACTING INFORMATION

ACTING INFORMATION (in each tablet)

Pantoprazole 20mg (as sodium sesquihydrate)

USES

- Frequent heartburn (more than twice a week)
- Stomach acid complaints due to GORD

WARNINGS

- ! This preparation is to be the relief of minor and temporary ailments and should be used strictly as directed.
- ! If symptoms persist, worsen or recur within two weeks of completing the course, consult a doctor.
- ! Ask your doctor or pharmacist before use if you are taking other medicines regularly.
- ! Please read the Consumer Medicine Information before use, which is available at www.takeda.com/en-au.

Do not use if:

- You are pregnant or breastfeeding or may become pregnant whilst taking this preparation except on medical advice.
- You are allergic to pantoprazole or other proton pump inhibitors.

OTHER INFORMATION

Store below 30°C

Not intended for immediate relief.

Use strictly as directed.

Do not take beyond 14 days without consulting your doctor.

Take for at least 7 days and up to 14 days.

Swallow the tablet whole with water, with or without food.

Take one tablet daily. Do not crush or chew the tablet.

Adults 18 years of age and over:

DIRECTIONS FOR USE

WARNINGS (continued)

Do not use if (continued):

- You have a severe liver disease or cirrhosis.
- You are taking aetzanavir (an anti-viral medication).
- You are under 18 years of age.
- The expiry date has passed or the blister is damaged.

Does not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Somac[®] Heartburn Relief
pantoprazole 20 mg (as sodium sesquihydrate)

14 Enteric-coated tablets

PHARMACIST ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Somac[®] Heartburn Relief
pantoprazole 20 mg (as sodium sesquihydrate)

14 Enteric-coated tablets

Each enteric-coated tablet contains:
pantoprazole 20 mg (as sodium sesquihydrate)

For lasting relief of frequent heartburn & stomach acid complaints due to gastro-oesophageal reflux disease (GORD)

AUST R 154252

Takeda Pharmaceuticals Australia Pty Ltd,
Sydney, Australia
www.takeda.com/en-au
SOMAC[®] is a registered trademark of Takeda GmbH

ONCE-DAILY Dosing
LASTING RELIEF

Takeda

9 335311 005026

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] HEARTBURN RELIEF (PANTOPRAZOLE SODIUM SESQUIHYDRATE)

1 NAME OF THE MEDICINE

Pantoprazole (as pantoprazole sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC Heartburn Relief enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SOMAC Heartburn Relief enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SOMAC Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on Vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption such as the elderly and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions or if respective clinical symptoms are observed. Rare cases of cyanocobalamin deficiency following acid-blocking therapy have been reported.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

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

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

See Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4 Special Warnings and Precautions For Use; Influence on Vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; special populations.

Paediatric use

To date there has been limited experience with treatment in children.

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.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see Section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listed in descending order of frequency

(Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$, not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating
 Rare: fever, peripheral oedema, and increased body temperature
 Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension
 Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness
 Rare: taste disorders, metallic taste
 Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort
 Rare: rectal disorder and colonic polyp
 Very rare: faecal discolouration and increased saliva
 Not known: flatulence, severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased
 Rare: bilirubin increased
 Very rare: hepatocellular failure, cholestatic hepatitis and jaundice
 Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes
 Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia
 Very rare: pain including skeletal pain
 Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption

Rare: angioedema and urticaria

Very rare: severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. Treatment should be symptomatic and supportive measures should be utilised. For information on the management of overdosage, contact the Poisons Information centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES****Mechanism of action**

Pantoprazole is a proton pump inhibitor (PPI). Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. It inhibits specifically and dose-proportionately

H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in [Table 1](#).

Table 1 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20 mg	Placebo	P	pantoprazole 20 mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

Special populations

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and $C_{\max}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

6.2 INCOMPATIBILITIES

Please see Section 4.5 - Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

SOMAC Heartburn Relief 20 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 2s, 7s and 14s.

*Not all pack sizes may be marketed

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

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

CAS number

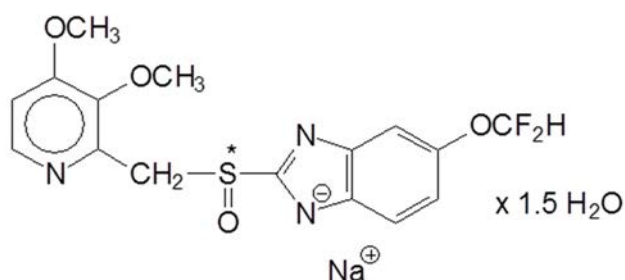
Chemical name (CAS) Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1\frac{1}{2}H_2O$

CAS number: 164579-32-2

Molecular weight: 432.4 (sodium salt x 1.5 H_2O)

Structural formula:



7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacy Only Medicine (Schedule 2) – 2* and 7 tablets

Pharmacist Only Medicine (Schedule 3) – 14 tablets

*Not all pack sizes may be marketed

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

Pharmacy Only Medicine (Schedule 2) – 27 February 2015

Pharmacist Only Medicine (Schedule 3) – 1 August 2008

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] HEARTBURN RELIEF (PANTOPRAZOLE SODIUM SESQUIHYDRATE)

1 NAME OF THE MEDICINE

Pantoprazole (as pantoprazole sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC Heartburn Relief enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SOMAC Heartburn Relief enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SOMAC Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on Vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption such as the elderly and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions or if respective clinical symptoms are observed. Rare cases of cyanocobalamin deficiency following acid-blocking therapy have been reported.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

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

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

See Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4 Special Warnings and Precautions For Use; Influence on Vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; special populations.

Paediatric use

To date there has been limited experience with treatment in children.

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.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see Section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listed in descending order of frequency

(Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$, not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating
 Rare: fever, peripheral oedema, and increased body temperature
 Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension
 Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness
 Rare: taste disorders, metallic taste
 Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort
 Rare: rectal disorder and colonic polyp
 Very rare: faecal discolouration and increased saliva
 Not known: flatulence, severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased
 Rare: bilirubin increased
 Very rare: hepatocellular failure, cholestatic hepatitis and jaundice
 Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes
 Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia
 Very rare: pain including skeletal pain
 Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption

Rare: angioedema and urticaria

Very rare: severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. Treatment should be symptomatic and supportive measures should be utilised. For information on the management of overdosage, contact the Poisons Information centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES****Mechanism of action**

Pantoprazole is a proton pump inhibitor (PPI). Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. It inhibits specifically and dose-proportionately

H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 1.

Table 1 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20 mg	Placebo	P	pantoprazole 20 mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

Special populations

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

6.2 INCOMPATIBILITIES

Please see Section 4.5 - Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

SOMAC Heartburn Relief 20 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 2s, 7s and 14s.

*Not all pack sizes may be marketed

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

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

CAS number

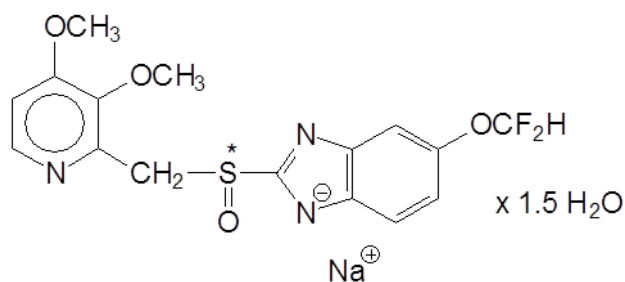
Chemical name (CAS) Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide sesquihydrate

Molecular formula: $C_{16} H_{14} F_2 N_3 NaO_4 S \cdot 1\frac{1}{2} H_2O$

CAS number: 164579-32-2

Molecular weight: 432.4 (sodium salt x 1.5 H_2O)

Structural formula:



7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacy Only Medicine (Schedule 2) – 2* and 7 tablets

Pharmacist Only Medicine (Schedule 3) – 14 tablets

*Not all pack sizes may be marketed

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

Pharmacy Only Medicine (Schedule 2) – 27 February 2015

Pharmacist Only Medicine (Schedule 3) – 1 August 2008

10 DATE OF REVISION

TBC

Summary table of changes

Section changed	Summary of new information
4.4	Addition of Subacute Cutaneous Lupus Erythematosus

Somac[®] Heartburn Relief Tablets

pantoprazole sodium sesquihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Somac Heartburn Relief.

It does not contain all the available information. It does not take the place of talking to your pharmacist or doctor.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available.

You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

Those updates may contain important information about the medicine and its use of which you should be aware.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac Heartburn Relief is used for

Somac Heartburn Relief is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux disease (GORD).

These symptoms can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Frequent heartburn is when you have heartburn for two or more days a week. Heartburn that occurs frequently is a typical symptom of GORD.

Somac Heartburn Relief is not the right medicine for you if you suffer heartburn only occasionally (one

episode of heartburn a week or less), or if you want immediate relief of heartburn.

Somac Heartburn Relief will start to suppress acid within a few hours, however it is not intended to provide instant symptom relief. For effective, lasting relief, you should take a full course of Somac Heartburn Relief (see ‘How to take Somac Heartburn Relief’ below).

Somac Heartburn Relief belongs to a group of medicines called proton pump inhibitors (PPIs). This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms.

Somac Heartburn Relief is not addictive.

Somac Heartburn Relief is for use by adults over 18 years of age.

Do not give Somac Heartburn Relief to children or adolescents under 18 years of age.

Before you start to take Somac Heartburn Relief

When you must not take it

Do not take Somac Heartburn Relief if you:

- **have an allergy to pantoprazole, any other PPI (such as omeprazole, rabeprazole or lansoprazole) or any of the ingredients listed at the end of this leaflet.** Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.
- **have severe liver disease or cirrhosis**
- **have recently had trouble swallowing, pain when swallowing, persistent vomiting**

or experienced unintended weight loss

- **have recently vomited blood, had black stools or notice blood in your stools**
- **are taking atazanavir or nelfinavir (anti-viral medications)**
- **are pregnant, intend to become pregnant, are breast-feeding or wish to start breast-feeding.**

Do not take it after the expiry date (EXP) printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to take it

Tell your pharmacist or doctor if you have:

- **jaundice, liver problems or anaemia**
- **a feeling of weakness or you look pale**
- **previously taken heartburn / indigestion medications continuously for 4 or more weeks**
- **persisting heartburn symptoms despite taking Somac Heartburn Relief (or other similar medicines) continuously for 2 weeks, or your symptoms have recently changed**
- **been told by your doctor that you have a stomach ulcer, or gastrointestinal surgery is planned**
- **heartburn/ indigestion symptoms for the first time and you are over 40 years of age**
- **a scheduled endoscopy** (investigation of your stomach lining performed by a specialist)
- **any allergies to any medicines or other substances, such as foods, preservatives or dyes.**

Your pharmacist or doctor can provide specific advice on whether

you should take Somac Heartburn Relief.

Tell your pharmacist or doctor if you have or have had any other medical conditions, or you are pregnant, intend to become pregnant, are breast-feeding or wish to start breast-feeding.

Taking other medicines

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

Some medicines and Somac Heartburn Relief may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (blood thinners)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infections
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Heartburn Relief, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your pharmacist or doctor has more information on medicines to be careful with or to avoid while taking Somac Heartburn Relief.

How to take Somac Heartburn Relief

The directions for use are included on the Medicine Information panel on the pack.

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

Follow all directions given to you by your pharmacist or doctor. They may differ from the information contained in this leaflet.

How to take it

Take one Somac Heartburn Relief tablet every day (once every 24 hours).

Swallow your tablets whole with a little water, with or without food.

Do not crush or chew the tablets. Somac Heartburn Relief tablets have a special coating to protect them from the acid contents of your stomach. For Somac Heartburn Relief to work effectively, this coating must not be broken.

How long to take it

For effective, lasting relief, take Somac Heartburn Relief strictly according to the directions on your pack.

Somac Heartburn Relief tablets should be taken for at least seven days, and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take it for longer than 7 days, ask your pharmacist for advice.

Do not take beyond 14 days without consulting your doctor.

Somac Heartburn Relief is not intended to provide instant relief from your heartburn/ indigestion symptoms.

If you are not sure, ask your pharmacist or doctor how to take your medicine.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

Do not take a double dose to make up for the dose that you missed. This may increase the chance of you getting an unwanted side effect.

If you are not sure what to do, ask your pharmacist or doctor.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre for advice (telephone Australia 13 11 26 or New Zealand 0800 764 766), go to Accident and Emergency at your nearest hospital, if you or anyone else may have taken too much Somac Heartburn Relief. Do this even if there are no signs of discomfort or poisoning.

Urgent medical attention may be needed.

While you are taking Somac Heartburn Relief

Things you must do

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery or an endoscopy, tell your doctor that you are taking Somac Heartburn Relief.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

Tell your doctor or pharmacist if you do not feel better while taking Somac Heartburn Relief. If your symptoms recur within 2 weeks of completing your course, consult your doctor.

Further investigation may be recommended.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Things you must not do

Somac Heartburn Relief may cause dizziness and visual disturbances. If affected, do not drive or operate machinery.

Things that may help your condition

Some self-help measures suggested below may help your condition. Your pharmacist or doctor can provide more information about these measures.

- **Alcohol** – you may be advised to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, headaches** - these medicines may irritate the stomach and may make your heartburn/indigestion symptoms worse. Your pharmacist or doctor may suggest other medicines you can take.
- **Caffeine** - you may be advised to limit the number of drinks which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** - eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **Smoking** - it is advisable for you to stop smoking or at least cut down.
- **Weight** - you may be advised that losing some weight will help your reflux/ indigestion symptoms.

Side effects

All medicines have some unwanted side effects. Sometimes they are serious, but most of the time they are not.

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

Tell your pharmacist or doctor if you notice any of the following while taking Somac Heartburn Relief and they worry you:

- headache or dizziness
- diarrhoea, constipation, nausea or vomiting
- pain, discomfort or excessive gas in the stomach or bowel

- indigestion
- mild weakness, tiredness or sleep disturbances
- increased sweating or body temperature
- blurred vision, dry mouth
- metallic taste
- mild skin reactions such as itchiness and rash

These are the more common side effects of Somac Heartburn Relief. It helps most people with heartburn/indigestion, but it has been uncommonly associated with such unwanted side effects.

See your pharmacist or doctor immediately if you notice any of the following:

- unusual tiredness, weakness, dizziness or fainting
- chest pain, fast heartbeat, shortness of breath
- loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine or bowel movements
- blood in the urine
- increased or decreased need to urinate
- bleeding or bruising more easily than normal
- skin problems such as itchiness and rash or swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent symptoms of infections such as fever, severe chills, sore throat or mouth ulcers
- high blood pressure
- water retention, swelling
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium levels in your blood

- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare or very rare.

Tell your pharmacist or doctor if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

Ask your pharmacist or doctor if you do not understand some of the information in this list.

After taking Somac Heartburn Relief

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 the medicine in a cool dry place where the temperature stays below 30°C.

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where 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 you stop taking this medicine or if 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

Somac Heartburn Relief is available as a 20 mg tablet. The tablets have an acid-resistant coating called an enteric coating.

The tablets are yellow and oval shaped, marked with 'P20' on one side.

Somac Heartburn Relief tablets are available in blister packs containing 7 and 14 tablets.

Ingredients

Somac Heartburn Relief tablets contain the equivalent of 20 mg pantoprazole.

Somac Heartburn Relief tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone
- povidone
- calcium stearate
- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode monogramming ink S-1-16530 Brown

Somac Heartburn Relief tablets do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac Heartburn Relief tablets are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney 2000
Ph: 1800 675 957

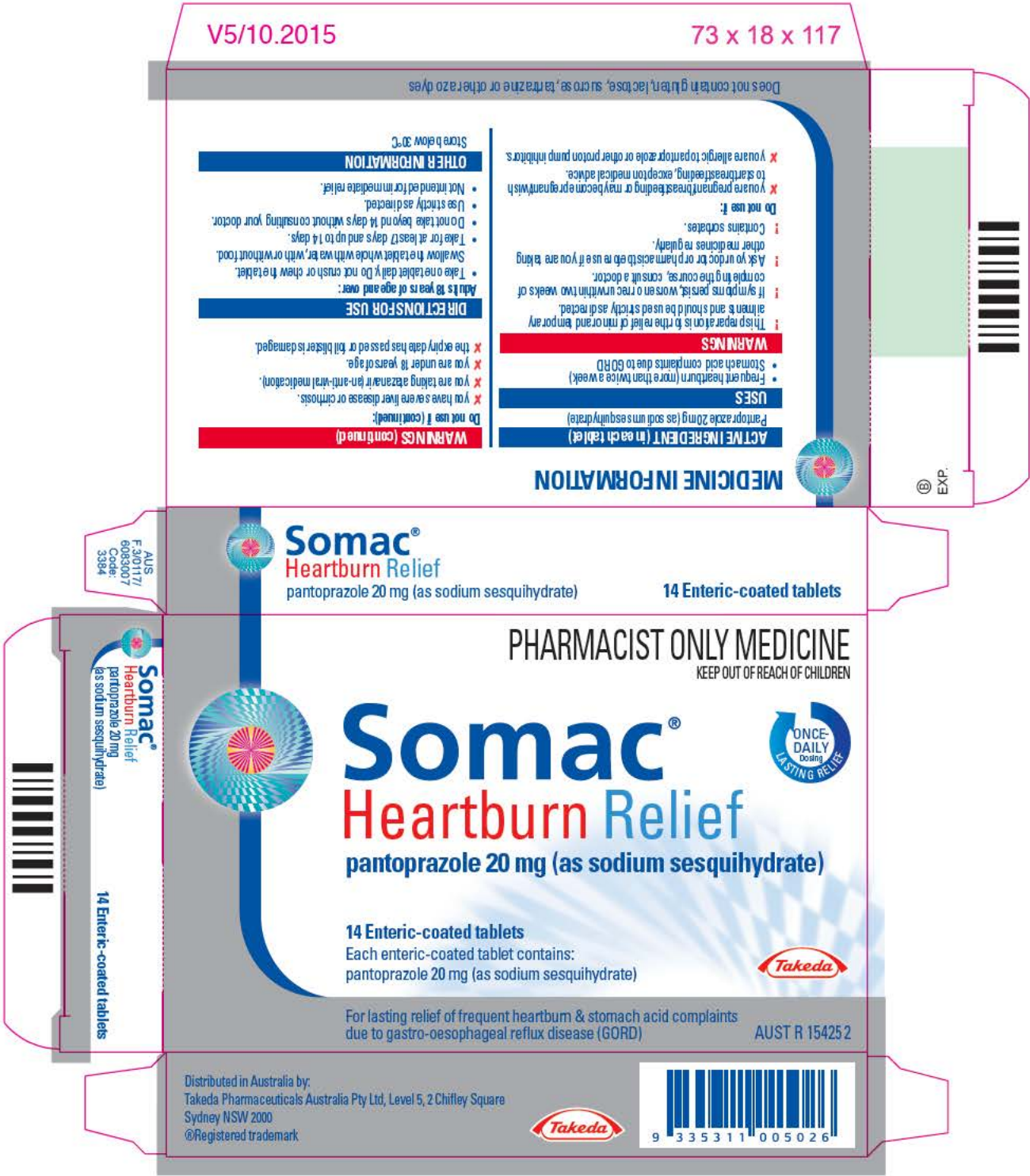
Australian Registration Numbers

Pharmacy Only Medicine (7 tablets) –
AUST R 234279

Pharmacist Only Medicine (14 tablets)
AUST R 154252

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This leaflet was prepared in TBC.

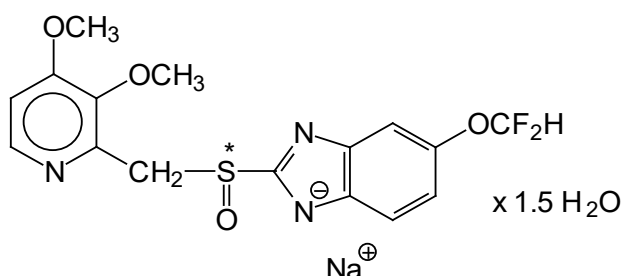


PRODUCT INFORMATION

SOMAC[®] HEARTBURN RELIEF TABLETS

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole (as pantoprazole sodium sesquihydrate)
Chemical name (CAS)	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S.1½ H ₂ O
CAS number:	164579-32-2
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

SOMAC Heartburn Relief enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole.

In addition to pantoprazole sodium, the tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor (PPI). It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($\text{pH} < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 $\mu\text{g/mL}$. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 1.

Table 1: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20mg	Placebo	P	pantoprazole 20mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

INDICATIONS

Somac Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption such as the elderly and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions or if respective clinical symptoms are observed. Rare cases of cyanocobalamin deficiency following acid-blocking therapy have been reported.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure.

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.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

Adverse effects such as dizziness and visual disturbances have been reported (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (in vitro) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL

cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in Pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in Lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there has been limited experience with treatment in children.

Effects on ability to drive and use machines

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4

are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see CONTRAINDICATIONS).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and

prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

ADVERSE EFFECTS

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listed in descending order of frequency (Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$, not known: cannot be estimated from the available data). These include the following

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating
Rare: fever, peripheral oedema, and increased body temperature
Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension
Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness
Rare: taste disorders, metallic taste
Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort
Rare: rectal disorder and colonic polyp
Very rare: faecal discolouration and increased saliva
Not known: flatulence, severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased
Rare: bilirubin increased
Very rare: hepatocellular failure, cholestatic hepatitis and jaundice
Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption

Rare: angioedema and urticaria

Very rare: severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

DOSAGE AND ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. Treatment should be symptomatic and supportive measures should be utilised. For information on the management of overdosage, contact the Poisons Information centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

SOMAC Heartburn Relief 20 mg tablets are available in blister packs of 2s, 7s and 14s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side.

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Pharmacy Only Medicine (Schedule 2) – 2* and 7 tablets

Pharmacist Only Medicine (Schedule 3) – 14 tablets

*Not all pack sizes may be marketed

DATE OF FIRST INCLUSION IN THE ARTG

Pharmacy Only Medicine (Schedule 2) – 27 February 2015

Pharmacist Only Medicine (Schedule 3) – 1 August 2008

DATE OF MOST RECENT AMENDMENT

®Registered trademark

Somac[®] Heartburn Relief Tablets

pantoprazole

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Somac Heartburn Relief.

It does not contain all the available information. It does not take the place of talking to your pharmacist or doctor.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available.

You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

Those updates may contain important information about the medicine and its use of which you should be aware.

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

Keep this leaflet with the medicine. You may need to read it again.

What Somac Heartburn Relief is used for

Somac Heartburn Relief is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux disease (GORD).

These symptoms can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Frequent heartburn is when you have heartburn for two or more days a week. Heartburn that occurs frequently is a typical symptom of GORD.

Somac Heartburn Relief is not the right medicine for you if you suffer heartburn only occasionally (one

episode of heartburn a week or less), or if you want immediate relief of heartburn.

Somac Heartburn Relief will start to suppress acid within a few hours, however it is not intended to provide instant symptom relief. For effective, lasting relief, you should take a full course of Somac Heartburn Relief (see ‘How to take Somac Heartburn Relief’ below).

Somac Heartburn Relief belongs to a group of medicines called proton pump inhibitors (PPIs). This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms.

Somac Heartburn Relief is not addictive.

Somac Heartburn Relief is for use by adults over 18 years of age.

Do not give Somac Heartburn Relief to children or adolescents under 18 years of age.

Before you start to take Somac Heartburn Relief

When you must not take it

Do not take Somac Heartburn Relief if you:

- **have an allergy to pantoprazole, any other PPI (such as omeprazole, rabeprazole or lansoprazole) or any of the ingredients listed at the end of this leaflet.** Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.
- **have severe liver disease or cirrhosis**
- **have recently had trouble swallowing, pain when swallowing, persistent vomiting**

or experienced unintended weight loss

- **have recently vomited blood, had black stools or notice blood in your stools**
- **are taking atazanavir or nelfinavir (anti-viral medications)**
- **are pregnant, intend to become pregnant, are breast-feeding or wish to start breast-feeding.**

Do not take it after the expiry date (EXP) printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to take it

Tell your pharmacist or doctor if you have:

- **jaundice, liver problems or anaemia**
- **a feeling of weakness or you look pale**
- **previously taken heartburn / indigestion medications continuously for 4 or more weeks**
- **persisting heartburn symptoms despite taking Somac Heartburn Relief (or other similar medicines) continuously for 2 weeks, or your symptoms have recently changed**
- **been told by your doctor that you have a stomach ulcer, or gastrointestinal surgery is planned**
- **heartburn/ indigestion symptoms for the first time and you are over 40 years of age**
- **a scheduled endoscopy** (investigation of your stomach lining performed by a specialist)
- **any allergies to any medicines or other substances, such as foods, preservatives or dyes.**

Your pharmacist or doctor can provide specific advice on whether

you should take Somac Heartburn Relief.

Tell your pharmacist or doctor if you have or have had any other medical conditions, or you are pregnant, intend to become pregnant, are breast-feeding or wish to start breast-feeding.

Taking other medicines

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

Some medicines and Somac Heartburn Relief may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (blood thinners)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infections
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Heartburn Relief, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your pharmacist or doctor has more information on medicines to be careful with or to avoid while taking Somac Heartburn Relief.

How to take Somac Heartburn Relief

The directions for use are included on the Medicine Information panel on the pack.

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

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

They may differ from the information contained in this leaflet.

How to take it

Take one Somac Heartburn Relief tablet every day (once every 24 hours).

Swallow your tablets whole with a little water, with or without food.

Do not crush or chew the tablets. Somac Heartburn Relief tablets have a special coating to protect them from the acid contents of your stomach. For Somac Heartburn Relief to work effectively, this coating must not be broken.

How long to take it

For effective, lasting relief, take Somac Heartburn Relief strictly according to the directions on your pack.

Somac Heartburn Relief tablets should be taken for at least seven days, and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take it for longer than 7 days, ask your pharmacist for advice.

Do not take beyond 14 days without consulting your doctor.

Somac Heartburn Relief is not intended to provide instant relief from your heartburn/ indigestion symptoms.

If you are not sure, ask your pharmacist or doctor how to take your medicine.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

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

This may increase the chance of you getting an unwanted side effect.

If you are not sure what to do, ask your pharmacist or doctor.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre for advice (telephone Australia 13 11 26 or New Zealand 0800 764 766), go to Accident and Emergency at your nearest hospital, if you or anyone else may have taken too much Somac Heartburn Relief. Do this even if there are no signs of discomfort or poisoning.

Urgent medical attention may be needed.

While you are taking Somac Heartburn Relief

Things you must do

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery or an endoscopy, tell your doctor that you are taking Somac Heartburn Relief.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

Tell your doctor or pharmacist if you do not feel better while taking Somac Heartburn Relief. If your symptoms recur within 2 weeks of completing your course, consult your doctor.

Further investigation may be recommended.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Things you must not do

Somac Heartburn Relief may cause dizziness and visual disturbances. If affected, do not drive or operate machinery.

Things that may help your condition

Some self-help measures suggested below may help your condition. Your pharmacist or doctor can provide more information about these measures.

- **Alcohol** – you may be advised to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, headaches** - these medicines may irritate the stomach and may make your heartburn/indigestion symptoms worse. Your pharmacist or doctor may suggest other medicines you can take.
- **Caffeine** - you may be advised to limit the number of drinks which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** - eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **Smoking** - it is advisable for you to stop smoking or at least cut down.
- **Weight** - you may be advised that losing some weight will help your reflux/indigestion symptoms.

Side effects

All medicines have some unwanted side effects. Sometimes they are serious, but most of the time they are not.

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

Tell your pharmacist or doctor if you notice any of the following while taking Somac Heartburn Relief and they worry you:

- headache or dizziness
- diarrhoea, constipation, nausea or vomiting
- pain, discomfort or excessive gas in the stomach or bowel

- indigestion
- mild weakness, tiredness or sleep disturbances
- increased sweating or body temperature
- blurred vision, dry mouth
- metallic taste
- mild skin reactions such as itchiness and rash

These are the more common side effects of Somac Heartburn Relief. It helps most people with heartburn/indigestion, but it has been uncommonly associated with such unwanted side effects.

See your pharmacist or doctor immediately if you notice any of the following:

- unusual tiredness, weakness, dizziness or fainting
- chest pain, fast heartbeat, shortness of breath
- loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine or bowel movements
- blood in the urine
- increased or decreased need to urinate
- bleeding or bruising more easily than normal
- skin problems such as itchiness and rash or swelling, blistering or peeling of the skin
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent symptoms of infections such as fever, severe chills, sore throat or mouth ulcers
- high blood pressure
- water retention, swelling
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been

associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare or very rare.

Tell your pharmacist or doctor if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

Ask your pharmacist or doctor if you do not understand some of the information in this list.

After taking Somac Heartburn Relief

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 the medicine in a cool dry place where the temperature stays below 30°C.

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where 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 you stop taking this medicine or if 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

Somac Heartburn Relief is available as a 20 mg tablet. The tablets have an acid-resistant coating called an enteric coating.

The tablets are yellow and oval shaped, marked with 'P20' on one side.

Somac Heartburn Relief tablets are available in blister packs containing 7 and 14 tablets.

Ingredients

Somac Heartburn Relief tablets contain the equivalent of 20 mg pantoprazole.

Somac Heartburn Relief tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone
- povidone
- calcium stearate
- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode monogramming ink S-1-16530 Brown

Somac Heartburn Relief tablets do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac Heartburn Relief tablets are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

2-4 Lyonpark Road

Macquarie Park NSW 2113

Ph: 1800 675 957

Australian Registration Numbers

Pharmacy Only Medicine (7 tablets) –
AUST R 234279

Pharmacist Only Medicine (14 tablets)
- AUST R 154252

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This leaflet was prepared in
May 2015

AUSTRALIAN PRODUCT INFORMATION

SOMAC[®] HEARTBURN RELIEF (PANTOPRAZOLE SODIUM SESQUIHYDRATE)

1 NAME OF THE MEDICINE

Pantoprazole (as pantoprazole sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMAC Heartburn Relief enteric coated tablets, each tablet contains 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SOMAC Heartburn Relief enteric coated tablets are yellow and oval shaped, marked with the letter "P20" on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SOMAC Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2 DOSE AND METHOD OF ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Influence on Vitamin B₁₂ absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ absorption such as the elderly and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions or if respective clinical symptoms are observed. Rare cases of cyanocobalamin deficiency following acid-blocking therapy have been reported.

Bone fracture

PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Acute Interstitial Nephritis

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

Hypomagnesaemia

Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. 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

General Toxicity

Gastrointestinal system

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity

Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in the elderly

See Sections 4.2 Dose and Method of Administration; Use in the elderly, 4.4 Special Warnings and Precautions For Use; Influence on Vitamin B₁₂ absorption, and 5.2 Pharmacokinetic Properties; special populations.

Paediatric use

To date there has been limited experience with treatment in children.

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.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyl oestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Drugs with pH-Dependent Absorption Pharmacokinetics

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

HIV Protease Inhibitors

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir or nelfinavir (see Section 4.3 Contraindications).

Mycophenolate mofetil

Co-administration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce the 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 pantoprazole with caution in transplant patients receiving mycophenolate mofetil.

Methotrexate

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Drugs that Inhibit or Induce CYP2C19 (tacrolimus, fluvoxamine)

Concomitant administration of pantoprazole 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 of pantoprazole.

Coumarin anticoagulants (phenprocoumon or warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or international normalised ratio (INR). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced foetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unknown. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the foetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Excretion into human milk has been reported. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as

dizziness and visual disturbances may occur (see Section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listed in descending order of frequency

(Very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$, not known: cannot be estimated from the available data). These include the following:

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating

Rare: fever, peripheral oedema, and increased body temperature

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders, metallic taste

Very rare: reduced movement and speech disorder, changes to the senses of smell and taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: flatulence, severe eructation, withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes
 Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 Special Warnings and Precautions for Use)).

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia
 Very rare: pain including skeletal pain
 Not known: fracture of wrist, hip and spine

Renal and urinary disorders

Very rare: interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis
 Very rare: leukopaenia, thrombocytopaenia, pancytopaenia

Psychiatric disorders

Uncommon: sleep disorders
 Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence
 Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Reproductive system and breast disorders

Rare: gynaecomastia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption
 Rare: angioedema and urticaria
 Very rare: severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity
 Unknown: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS)

Eye disorders

Uncommon: disturbances in vision (blurred vision)
 Very rare: conjunctivitis

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 <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable. Treatment should be symptomatic and supportive measures should be utilised. For information on the management of overdosage, contact the Poisons Information centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pantoprazole is a proton pump inhibitor (PPI). Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Clinical trials

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in [Table 1](#).

Table 1 Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20 mg	Placebo	P	pantoprazole 20 mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL. Terminal half-life is approximately 1 h. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

Distribution

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system.

Excretion

Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

Special populations

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialysable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet also contains sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S 1-16530 Brown.

6.2 INCOMPATIBILITIES

Please see Section 4.5 - Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

SOMAC Heartburn Relief 20 mg tablets are available in:

- Aluminium/aluminium (Al/Al) blister packs of 2s, 7s and 14s.

*Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

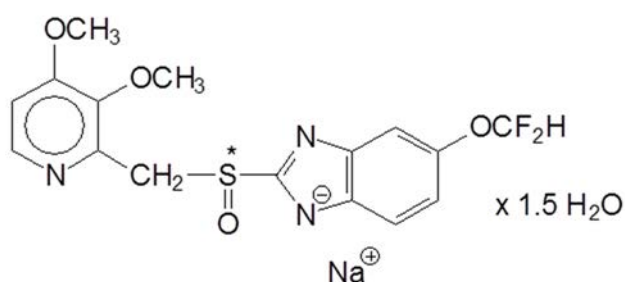
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

CAS number

Chemical name (CAS)	Sodium-[5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S.1½ H ₂ O
CAS number:	164579-32-2
Molecular weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacy Only Medicine (Schedule 2) – 2* and 7 tablets

Pharmacist Only Medicine (Schedule 3) – 14 tablets

*Not all pack sizes may be marketed

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

Pharmacy Only Medicine (Schedule 2) – 27 February 2015

Pharmacist Only Medicine (Schedule 3) – 1 August 2008

10 DATE OF REVISION

XXXXXX

Summary table of changes

Section changed	Summary of new information
4.4	Addition of Subacute Cutaneous Lupus Erythematosus
4.8	Addition of TGA requested text (rebound acid hypersecretion)
4.4 & 4.8	Addition of hypocalcaemia, hypokalaemia and DRESS.
4.8	Addition of Subacute Cutaneous Lupus Erythematosus

SOMAC HEARTBURN RELIEF® is a registered trademark of Takeda GmbH.

Somac[®] Heartburn Relief Tablets

pantoprazole sodium sesquihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Somac Heartburn Relief.

It does not contain all the available information. It does not take the place of talking to your pharmacist or doctor.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available.

You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine.

Those updates may contain important information about the medicine and its use of which you should be aware.

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

Keep this leaflet with the medicine.

You may need to read it again.

What Somac Heartburn Relief is used for

Somac Heartburn Relief is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux disease (GORD).

These symptoms can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Frequent heartburn is when you have heartburn for two or more days a week. Heartburn that occurs frequently is a typical symptom of GORD.

Somac Heartburn Relief is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

Somac Heartburn Relief will start to suppress acid within a few hours, however it is not intended to provide instant symptom relief. For effective, lasting relief, you should take a full course of Somac Heartburn Relief (see 'How to take Somac Heartburn Relief' below).

Somac Heartburn Relief belongs to a group of medicines called proton pump inhibitors (PPIs). This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms.

Somac Heartburn Relief is not addictive.

Somac Heartburn Relief is for use by adults over 18 years of age.

Do not give Somac Heartburn Relief to children or adolescents under 18 years of age.

Before you start to take Somac Heartburn Relief

When you must not take it

Do not take Somac Heartburn Relief if you:

- have an allergy to pantoprazole, any other PPI (such as omeprazole, rabeprazole or lansoprazole) or any of the ingredients listed at the end of this leaflet.

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

- have severe liver disease or cirrhosis
- have recently had trouble swallowing, pain when swallowing, persistent vomiting or experienced unintended weight loss
- have recently vomited blood, had black stools or notice blood in your stools
- are taking atazanavir or nelfinavir (anti-viral medications)
- are pregnant, intend to become pregnant, are breast-feeding or wish to start breast-feeding.

Do not take it after the expiry date (EXP) printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to take it

Tell your pharmacist or doctor if you have:

- jaundice, liver problems or anaemia
- a feeling of weakness or you look pale
- previously taken heartburn / indigestion medications continuously for 4 or more weeks
- persisting heartburn symptoms despite taking Somac Heartburn Relief (or other similar medicines) continuously for 2 weeks, or your symptoms have recently changed
- been told by your doctor that you have a stomach ulcer, or gastrointestinal surgery is planned
- heartburn/ indigestion symptoms for the first time and you are over 40 years of age
- a scheduled endoscopy (investigation of your stomach lining performed by a specialist)
- any allergies to any medicines or other substances, such as foods, preservatives or dyes.

Your pharmacist or doctor can provide specific advice on whether you should take Somac Heartburn Relief.

Tell your pharmacist or doctor if you have or have had any other medical conditions, or you are pregnant, intend to become pregnant, are breast-feeding or wish to start breast-feeding.

Taking other medicines

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

Some medicines and Somac Heartburn Relief may interfere with each other. These include:

- warfarin, phenprocoumon - medicines used to prevent blood clots (blood thinners)
- atazanavir, nelfinavir – medicines used to treat viral infections such as HIV
- ketoconazole, itraconazole, posaconazole - medicines used to treat fungal infections
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- tacrolimus, mycophenolate mofetil – medicines used to suppress the immune system
- fluvoxamine - a medicine used to treat anxiety and depression

These medicines may be affected by Somac Heartburn Relief, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your pharmacist or doctor has more information on medicines to be careful with or to avoid while taking Somac Heartburn Relief.

How to take Somac Heartburn Relief

The directions for use are included on the Medicine Information panel on the pack.

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

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

They may differ from the information contained in this leaflet.

How to take it

Take one Somac Heartburn Relief tablet every day (once every 24 hours).

Swallow your tablets whole with a little water, with or without food.

Do not crush or chew the tablets.

Somac Heartburn Relief tablets have a special coating to protect them from the acid contents of your stomach. For Somac Heartburn Relief to work effectively, this coating must not be broken.

How long to take it

For effective, lasting relief, take Somac Heartburn Relief strictly according to the directions on your pack.

Somac Heartburn Relief tablets should be taken for at least seven days, and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take it for longer than 7 days, ask your pharmacist for advice.

Do not take beyond 14 days without consulting your doctor.

Somac Heartburn Relief is not intended to provide instant relief from your heartburn/ indigestion symptoms.

If you are not sure, ask your pharmacist or doctor how to take your medicine.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

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

This may increase the chance of you getting an unwanted side effect.

If you are not sure what to do, ask your pharmacist or doctor.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre for advice (telephone Australia 13 11 26 or New Zealand 0800 764 766), go to Accident and Emergency at your nearest hospital, if you or anyone else may have taken too much Somac Heartburn Relief. Do this even if there are no signs of discomfort or poisoning.

Urgent medical attention may be needed.

While you are taking Somac Heartburn Relief

Things you must do

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery or an endoscopy, tell your doctor that you are taking Somac Heartburn Relief.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

Tell your doctor or pharmacist if you do not feel better while taking Somac Heartburn Relief. If your symptoms recur within 2 weeks of completing your course, consult your doctor.

Further investigation may be recommended.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Things you must not do

Somac Heartburn Relief may cause dizziness and visual disturbances. If affected, do not drive or operate machinery.

Things that may help your condition

Some self-help measures suggested below may help your condition. Your pharmacist or doctor can provide more information about these measures.

- **Alcohol –**
you may be advised to limit your alcohol intake.
- **Aspirin and many other medicines used to treat arthritis, period pain, headaches –**
these medicines may irritate the stomach and may make your heartburn/ indigestion symptoms worse. Your pharmacist or doctor may suggest other medicines you can take.
- **Caffeine –**
you may be advised to limit the number of drinks which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits –**
eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **Smoking –**
it is advisable for you to stop smoking or at least cut down.
- **Weight –**
you may be advised that losing some weight will help your reflux/ indigestion symptoms.

Side effects

All medicines have some unwanted side effects. Sometimes they are serious, but most of the time they are not.

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

Tell your pharmacist or doctor if you notice any of the following while taking Somac Heartburn Relief and they worry you:

- headache or dizziness
- diarrhoea, constipation, nausea or vomiting
- pain, discomfort or excessive gas in the stomach or bowel
- indigestion
- mild weakness, tiredness or sleep disturbances
- increased sweating or body temperature
- blurred vision, dry mouth
- metallic taste
- mild skin reactions such as itchiness and rash

These are the more common side effects of Somac Heartburn Relief. It helps most people with heartburn/ indigestion, but it has been uncommonly associated with such unwanted side effects.

See your pharmacist or doctor immediately if you notice any of the following:

- unusual tiredness, weakness, dizziness or fainting
- chest pain, fast heartbeat, shortness of breath
- loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine or bowel movements
- blood in the urine
- increased or decreased need to urinate
- bleeding or bruising more easily than normal

- skin problems such as itchiness and rash or swelling, blistering or peeling of the skin or rash when exposed to the sun, possibly with pain in the joints
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing
- frequent symptoms of infections such as fever, severe chills, sore throat or mouth ulcers
- high blood pressure
- water retention, swelling
- depression, confusion or anxiety
- bone fracture of the hip, wrist or spine (mainly a risk in people who take high doses of PPIs or use them long term (a year or longer))
- symptoms such as seizures, abnormal or fast heartbeat or jerking/shaking movements. These can be a sign of low magnesium, calcium or potassium levels in your blood
- severe and/or persistent diarrhoea, because this medicine has been associated with a small increase in infectious diarrhoea

The above list includes serious side effects that may require medical attention. Serious side effects are rare or very rare.

Tell your pharmacist or doctor if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

Ask your pharmacist or doctor if you do not understand some of the information in this list.

After taking Somac Heartburn Relief

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 the medicine in a cool dry place where the temperature stays below 30°C.

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where 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 you stop taking this medicine or if 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

Somac Heartburn Relief is available as a 20 mg tablet. The tablets have an acid-resistant coating called an enteric coating.

The tablets are yellow and oval shaped, marked with 'P20' on one side.

Somac Heartburn Relief tablets are available in blister packs containing 7 and 14 tablets.

Ingredients

Somac Heartburn Relief tablets contain the equivalent of 20 mg pantoprazole.

Somac Heartburn Relief tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone
- povidone
- calcium stearate

- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode monogramming ink S-1-16530 Brown

Somac Heartburn Relief tablets do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac Heartburn Relief tablets are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

Level 5

2 Chifley Square

Sydney 2000

Ph: 1800 675 957

Australian Registration Numbers

Pharmacy Only Medicine (7 tablets)
– AUST R 234279

Pharmacist Only Medicine (14 tablets) AUST R 154252

SOMAC HEARTBURN RELIEF® is a registered trademark of Takeda GmbH.

This leaflet was prepared in June 2020

s22, s47

F1/01.2012

73 x 18 x 117

Carefully read the enclosed Consumer Medicine Information before use



Batch	Expiry date

14 ENTERIC-COATED TABLETS
Pantoprazole 20mg (as sodium sesquihydrate)

For lasting relief of frequent heartburn & stomach acid complaints due to gastro-oesophageal reflux

AUS F.1/
1112/
6083007

PHARMACIST ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Somac[®]
Heartburn Relief

14 ENTERIC-COATED TABLETS
Each enteric-coated tablet contains:
Pantoprazole 20mg (as sodium sesquihydrate)

For lasting relief of frequent heartburn & stomach acid complaints due to gastro-oesophageal reflux

AUST R 154252

Distributed in Australia by:
Takeda Pharmaceuticals Australia Pty Ltd, 2-4 Lyonpark Road, Macquarie Park, NSW 2113
® Registered trademark of Takeda GmbH
MADE IN GERMANY



Somac[®]
Heartburn Relief

14 ENTERIC-COATED TABLETS
Pantoprazole 20mg (as sodium sesquihydrate)

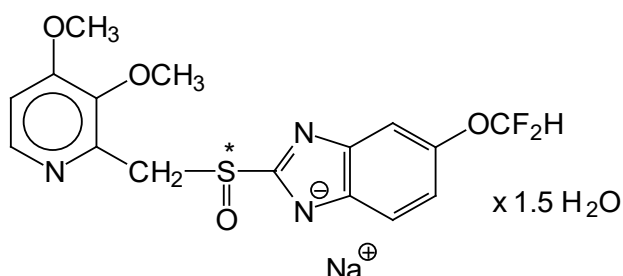
For lasting relief of frequent heartburn.

PRODUCT INFORMATION

SOMAC[®] HEARTBURN RELIEF TABLETS

NAME OF THE MEDICINE

Active ingredient:	Pantoprazole sodium (as pantoprazole sodium sesquihydrate)
Chemical Name (CAS)	Sodium-[5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate
Molecular Formula:	C ₁₆ H ₁₄ F ₂ N ₃ NaO ₄ S
CAS Number:	138 786-67-1 (pantoprazole sodium)
Molecular Weight:	432.4 (sodium salt x 1.5 H ₂ O)
Structural formula:	



DESCRIPTION

SOMAC Heartburn Relief enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole.

The molecular weight of pantoprazole, sodium salt x 1.5 H₂O is 432.4. Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

In addition to pantoprazole sodium, these tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow, propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Monogramming Ink S-1-16530 Brown.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion.

As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($\text{pH} < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H₂ receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 µg/mL. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

CLINICAL TRIALS

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 1.

Table 1: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20mg	Placebo	P	pantoprazole 20mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

INDICATIONS

Somac Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

CONTRAINDICATIONS

Known hypersensitivity to pantoprazole, substituted benzimidazoles or any other components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with atazanavir (see INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Pantoprazole, like all proton pump inhibitors, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B12) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption or if respective clinical symptoms are observed.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

Adverse effects such as dizziness and visual disturbances have been reported (see ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

Genotoxicity

A number of in vitro and in vivo genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the in vivo tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes in vitro, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis

Pantoprazole was found to be negative in the following studies: in vivo chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (in vitro) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in Pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in Lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Paediatric Use

To date there has been limited experience with treatment in children.

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyloestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants (e.g. warfarin or phenprocoumon), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Concomitant use of proton pump inhibitors with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole, itraconazole, posaconazole, erlotinib), might be altered due to the decrease in gastric acidity.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir.

The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see CONTRAINDICATIONS).

ADVERSE EFFECTS

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

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

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating

Rare: fever and peripheral oedema

Very rare: flushing, substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension

Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness

Rare: taste disorders

Very rare: reduced movement and speech disorder, changes to the sense of smell and taste

Not known: metallic taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal distension and bloating, abdominal pain and discomfort, constipation, dry mouth

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: flatulence, severe eructation

Hearing and vestibular disorders

Very rare: tinnitus

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased (transaminases, gamma GT)

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes

Not known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Renal and urinary disorders

Very rare: interstitial nephritis

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia, increased coagulation time

Psychiatric disorders

Uncommon: sleep disorders

Rare: depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption

Rare: angioedema and urticaria

Very rare: severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Reproductive system and breast disorders

Rare: gynaecomastia

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

DOSAGE AND ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. Treatment should be symptomatic and supportive measures should be utilised. For information on the management of overdosage, contact the Poisons Information centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

SOMAC Heartburn Relief 20 mg tablets are available in blister packs of 2s, 7s and 14s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side.

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S3 – Pharmacist Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

1 August 2008

DATE OF MOST RECENT AMENDMENT

XXXXXXX

® Registered trademark

Somac[®] Heartburn Relief Tablets

pantoprazole

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Somac Heartburn Relief.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. More recent information on the medicine may be available. You should ensure that you speak to your pharmacist or doctor to obtain the most up to date information on this medicine. **You can also download the most up to date leaflet from <http://www.takedaaustralia.com.au>.**

Those updates may contain important information about the medicine and its use of which you should be aware.

All medicines have risks and benefits. Your doctor or pharmacist has weighed the risks of you taking Somac Heartburn Relief against the benefits this medicine is expected to have for you.

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 Somac Heartburn Relief is used for

Somac Heartburn Relief is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by “washing back” (reflux) of food and acid from the stomach into the food pipe, also known as the oesophagus.

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

Frequent heartburn is when you have heartburn for two or more days a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Somac Heartburn Relief is recommended for adults over 18 years of age suffering from heartburn at least 2 times a week. Somac Heartburn Relief is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

This medicine belongs to a group of medicines called proton pump inhibitors (PPIs).

This medicine works by decreasing the amount of acid the stomach makes to give relief from the symptoms.

Somac Heartburn Relief will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take Somac Heartburn Relief for a few days before experiencing the full effect.

This medicine is not addictive. This medicine is available only from your pharmacist or your doctor.

This medicine is not expected to affect your ability to drive a car or operate machinery.

Somac Heartburn Relief should not be given to children and adolescents under 18 years of age. There is not enough information to recommend the use of this medicine for children and adolescents under 18 years of age.

Before you start to take Somac Heartburn Relief

When you must not take it

Do not take Somac Heartburn Relief if you have an allergy to:

- any medicine containing pantoprazole or any of the ingredients listed at the end of this leaflet.

Some symptoms of an allergic reaction include skin rash, itching, shortness of breath or swelling of the face, lips or tongue, which may cause difficulty in swallowing or breathing.

Do not take this medicine if you have severe liver disease or cirrhosis. Do not take Somac Heartburn Relief in combination with atazanavir (an anti-viral medication).

Do not take it after the expiry date (EXP) printed on the pack or if the packaging is damaged or shows signs of tampering.

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

Before you start to take it

Tell your doctor or pharmacist if you have any allergies to

- pantoprazole
- any other medicines or any other substances, such as foods, preservatives or dyes.

Tell your doctor if you have or have had any other medical conditions.

Tell your doctor if you are pregnant, intend to become pregnant, or are breast-feeding.

Your doctor can discuss the risks and benefits involved.

If you have not told your doctor or pharmacist about any of the above, tell them before you take Somac Heartburn Relief.

Talk to your doctor first before taking Somac Heartburn Relief if:

- you have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you have jaundice, liver problems, anaemia, difficulty swallowing, previous gastric ulcer or gastrointestinal surgery.
- you have new or recently changed symptoms including persistent vomiting or vomiting of blood, blood in the stools or unexplained weight loss.

If you have experienced any of the above you should see your doctor immediately. If you have suffered from frequent heartburn / indigestion symptoms for some time you should see your doctor.

You should also speak to your doctor before taking Somac Heartburn Relief if you are due to have an endoscopy (a special test ordered by your doctor).

Taking other medicines

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

Some medicines and Somac Heartburn Relief may interfere with each other. These include:

- warfarin - medicines used to prevent blood clots (anticoagulants)
- atazanavir – medicines used to treat viral infections such as HIV
- ketoconazole itraconazole, posaconazole - medicines used to treat fungal infection
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer

These medicines may be affected by Somac Heartburn Relief, or may affect how well it works. You may need to use different amounts of your medicine, or take different medicines.

Your doctor or pharmacist has more information on medicines to be careful

with or to avoid while taking Somac Heartburn Relief.

How to take Somac Heartburn Relief

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.

How much to take

Take one Somac Heartburn Relief tablet once a day (every 24 hours)

How and when to take it

Swallow your tablets whole with a little water with or without food.

Do not crush or chew the tablets. Somac Heartburn Relief tablets have a special coating to protect them from the acidic contents of your stomach. For Somac Heartburn Relief to work effectively, this coating must not be broken.

How long to take it

Somac Heartburn Relief tablets should be taken for at least seven days, and up to 14 days.

You should not take it for more than 14 days unless directed by a doctor.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

Do not take a double dose to make up for the dose that you missed. This may increase the chance of you getting an unwanted side effect.

If you are not sure what to do, ask your doctor or pharmacist.

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

If you take too much (overdose)

Immediately telephone your doctor or Poisons Information Centre for advice (telephone Australia 13 11 26 or New Zealand 0800 764 766), go to Accident and Emergency (Casualty) at your nearest hospital, if you or anyone else may have taken too much Somac Heartburn Relief. Do this even if there are no signs of discomfort or poisoning. Urgent medical attention may be needed.

While you are taking Somac Heartburn Relief

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking Somac Heartburn Relief.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you are going to have surgery, tell the surgeon that you are taking this medicine.

If you become pregnant while you are taking this medicine, tell your doctor or pharmacist immediately.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

It may interfere with the results of some tests.

Tell your doctor or pharmacist if you do not feel better while taking Somac Heartburn Relief

If symptoms persist or recur within 2 weeks of completing the course, consult a doctor.

Further investigation may be recommended.

Things that may help your condition

Some self help measures suggested below may help your condition. Your doctor or pharmacist can give you more information about these measures.

- **Alcohol** – you may be advised to limit your alcohol intake.

- **Aspirin and many other medicines used to treat arthritis, period pain, 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** - you may be advised to limit the number of drinks which contain caffeine, such as coffee, tea, cocoa and cola drinks, because they contain ingredients that may irritate your stomach.
- **Eating habits** - eat smaller, more frequent meals. Eat slowly and chew your food carefully. Try not to rush at meal times.
- **Smoking** - it is advisable for you to stop smoking or at least cut down.
- **Weight** - you may be advised that losing some weight will help your condition.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Somac Heartburn Relief.

It helps most people with peptic ulcers or reflux disease, but it may have unwanted side effects in a few people.

All medicines have some unwanted side effects. Sometimes they are serious, but 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 or pharmacist if you notice any of the following and they worry you:

- headache
- dizziness
- diarrhoea
- nausea or vomiting
- stomach pain
- excessive gas in the stomach or bowel

- indigestion
- constipation
- dry mouth
- metallic taste
- weakness or tiredness
- increased sweating
- blurred vision
- skin problems such as itchiness and rash

These are the more common side effects of Somac Heartburn Relief.

See your doctor immediately if you notice any of the following:

- unusual tiredness or weakness
- nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine.
- skin problems such as itchiness and rash, or swelling, blistering or peeling of the skin.
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing.
- frequent symptoms of infections such as fever, severe chills, sore throat or mouth ulcers
- chest pain
- shortness of breath
- high blood pressure
- swelling of the legs
- bleeding or bruising more easily than normal
- depression, confusion or anxiety

The above list includes serious side effects that may require medical attention. Serious side effects are rare.

Tell your doctor or pharmacist if you notice anything else that is making you feel unwell. Other side effects not listed above may occur in some people.

Ask your doctor or pharmacist if you do not understand some of the information in this list.

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

After taking Somac Heartburn Relief

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 the medicine in a cool dry place where the temperature stays below 30°C.

Do not store it or any other medicines in the bathroom, near a sink or windowsill. Do not leave it in the car.

Heat and dampness can destroy some medicines.

Keep it where 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 you stop taking this medicine or if 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

Somac Heartburn Relief is available as a 20 mg tablet. The tablets have an acid-resistant coating called an enteric coating.

The tablets are yellow and oval shaped, marked with 'P20' on one side.

Somac Heartburn Relief tablets are available in blister packs containing 2, 7 and 14 tablets.

Ingredients

Somac Heartburn Relief tablets contain the equivalent of 20 mg pantoprazole.

Somac Heartburn Relief tablets also contain:

- sodium carbonate anhydrous
- mannitol
- crospovidone
- povidone

- calcium stearate
- hypromellose
- titanium dioxide
- iron oxide yellow
- propylene glycol
- methacrylic acid copolymer
- polysorbate 80
- sodium lauryl sulfate
- triethyl citrate
- opacode monogramming ink S-1-16530 Brown

Somac Heartburn Relief tablets do not contain gluten, lactose, sucrose, tartrazine or other azo dyes.

Supplier

Somac Heartburn Relief tablets are made in Germany.

Somac Heartburn Relief tablets are supplied in Australia by:

Takeda Pharmaceuticals Australia Pty Ltd

2-4 Lyonpark Road

Macquarie Park NSW 2113

Ph: 1800 675 957

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Australian Registration Number(s)

Somac Heartburn Relief

AUST R 154252

PRODUCT INFORMATION

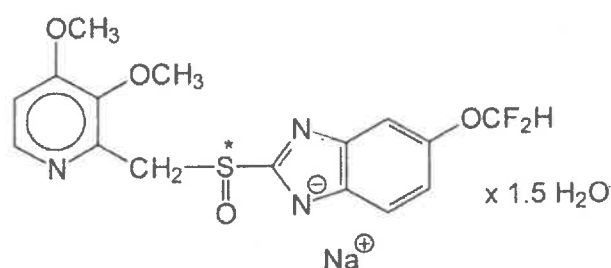
SOMAC[®] Heartburn Relief Tablets

NAME OF THE MEDICINE

Non-proprietary name: Pantoprazole sodium (as pantoprazole sodium sesquihydrate)

CAS Number: 138 786-67-1 (pantoprazole sodium)

The structure of pantoprazole sodium sesquihydrate is:



DESCRIPTION

SOMAC Heartburn Relief enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole.

The molecular weight of pantoprazole, sodium salt x 1.5 H₂O is 432.4. Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

In addition to pantoprazole sodium, these tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow (CI 77492), propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Brown S-1-16530 printing ink.

PHARMACOLOGY

Pharmacodynamics

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As

pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment ($\text{pH} < 3$), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 $\mu\text{g/mL}$. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

In patients with renal impairment (including those undergoing dialysis) no dose reduction is required. Although the main metabolite is moderately increased, there is no accumulation. The half-life of pantoprazole is as short as in healthy subjects. Pantoprazole is poorly dialyzable.

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

Clinical Trials

Treatment of symptomatic reflux (GORD)

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 1.

Table 1: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20mg	Placebo	P	pantoprazole 20mg	Placebo	P
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001
Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

INDICATIONS

Somac Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD)

CONTRAINDICATIONS

Pantoprazole may not be used in cases of known hypersensitivity to any components of the formulation, or in cases of cirrhosis or severe liver disease.

Pantoprazole, like other proton pump inhibitors, should not be co-administered with atazanavir (see **Interactions with other medicines**).

PRECAUTIONS

Patients should be referred to their doctor for review if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded.
- They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.

- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Genotoxicity: A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). In both species, pantoprazole exposure was high with the AUCs being 26 to 30 times higher in the rat or mouse respectively, than humans using the 20 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and none were detected in controls. No metastases of these carcinoids were detected. There was no increase in incidence of liver tumours. The dose of 15 mg/kg is seen to be the no-effect level for liver tumours in rodents.

Consideration of the possible mechanisms involved in the development of the above drug-related tumour types suggests that it is unlikely that there is any carcinogenic risk in humans at therapeutic dose levels of pantoprazole for short term treatment.

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Use in pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at ≥ 150 mg/kg/day and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

Use in lactation

A peri/post-natal study in rats found that treatment with pantoprazole at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children and adolescents under 18 years of age

To date there has been limited experience with treatment in children.

Interactions with other medicines

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinylloestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole), might be altered due to the decrease in gastric acidity.

Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see **Contraindications**).

ADVERSE EFFECTS

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole:

Body as a whole

Fatigue, asthenia and increased sweating

Rare reports of fever, anaphylactic reactions including anaphylactic shock and peripheral oedema

Very rare reports of substernal chest pain and hot flushes

Cardiovascular disorders general

Rare reports of hypertension

Very rare reports of circulatory collapse

Central and peripheral nervous system disorders

Headache

Uncommon reports of dizziness

Very rare reports of reduced movement and speech disorder

Gastrointestinal system disorders

Diarrhoea, severe eructation, constipation or flatulence, dry mouth, and upper abdominal pain

Uncommon reports of nausea and vomiting

Rare reports of rectal disorder and colonic polyp

Very rare reports of faecal discolouration and increased saliva

Hearing and vestibular disorders

Very rare reports of tinnitus

Liver and biliary system disorders

Rare reports of increased liver enzymes (transaminases, gamma-GT) have occurred in patients receiving long-term maintenance therapy.

Very rare reports of hepatic failure, cholestatic hepatitis, bilirubinaemia and jaundice

The occurrence of severe hepatocellular damage leading to jaundice or hepatic failure having a temporal relationship to the intake of pantoprazole has been reported with a frequency of approximately one in a million patients.

Metabolic and nutritional disorders

Rare reports of hypertriglyceridaemia

Musculoskeletal

Rare reports of myalgia and arthralgia

Very rare reports of pain including skeletal pain

Renal and urinary disorders

Very rare reports of interstitial nephritis

Platelet, bleeding, clotting disorders

Very rare reports of thrombocytopenia and increased coagulation time

Psychiatric disorders

Rare reports of onset of depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence

Very rare reports of anxiety

Red and white blood cell disorders

Rare reports of anaemia

Very rare reports of leukopenia

Resistance mechanism disorders

Rare reports of sepsis

Respiratory system disorders

Very rare reports of dyspnoea

Skin and appendages

Uncommon reports of allergic reactions such as pruritus and skin rash

Rare reports of angioedema and urticaria

Very rare reports of severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

Special senses, other disorders

Metallic taste

Very rare reports of changes to the senses of smell and taste

Vascular (extracardiac) disorders

Very rare reports of flushing

Vision disorders

Uncommon reports of disturbances in vision (blurred vision)

Very rare reports of conjunctivitis

DOSAGE AND ADMINISTRATION

SOMAC Heartburn Relief is indicated for use in adults 18 years of age and over. SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Contraindications). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

OVERDOSAGE

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated. Standard detoxification procedures apply. Contact the Poisons Information centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION

SOMAC Heartburn Relief 20 mg tablets are available in bottles or blister packs* of 2s, 7s and 14s. The tablets are yellow and oval shaped, marked with the letter "P20" on one side.

* Only blister packs are marketed.

SPONSOR

Nycomed Pty Ltd
ABN 71 095 610 870
2-4 Lyonpark Road

North Ryde NSW 2113
For medical enquiries, call (AUST) 1800 675 957

TGA Approval Date: 31 July 2008
Date of Most Recent Amendment: TBA

Poisons Schedule: S3 – Pharmacist Only Medicine

® Registered trademark of Nycomed GmbH

PRESCRIPTION ONLY MEDICINE

KEEP OUT OF REACH OF CHILDREN

Somac[®]
pantoprazole 40 mg

Powder for injection

Each vial contains: pantoprazole sodium
equivalent to pantoprazole 40 mg.

Contains no antimicrobial agent.

Use in one patient on one occasion only.

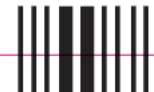
For IV use.

Directions for use: Refer to package insert.



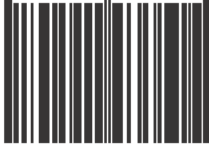
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Also contains disodium edetate 1 mg and sodium hydroxide 0.24 mg.

Directions for use:
Please refer to the enclosed package insert.

Store below 25°C.
Protect from light.

Contains no antimicrobial agent.

Use in one patient on one occasion only.



Somac®
pantoprazole 40 mg

**PRESCRIPTION ONLY
MEDICINE**
KEEP OUT OF REACH OF CHILDREN



Somac®
pantoprazole
40 mg

Each vial contains:
pantoprazole sodium
42.3 mg equivalent to
pantoprazole 40 mg

1 vial powder for injection
For intravenous use

AUST R 121427



Somac®
pantoprazole 40 mg

Distributed in
Australia by:
**Takeda
Pharmaceuticals
Australia Pty Ltd**
Level 5
2 Chifley Square
Sydney NSW 2000

®Registered
trademark of
Takeda GmbH



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Somac®
pantoprazole 40 mg

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PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Somac® 40 mg
pantoprazole
Powder for injection



Each vial contains:
pantoprazole sodium
equivalent to
pantoprazole 40 mg

Contains no antimicrobial
agent. Use in one patient
on one occasion only.
For IV use
Directions for use;
Refer to package insert

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PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Somac®
pantoprazole 40 mg



Powder for injection

Each vial contains: pantoprazole sodium
equivalent to pantoprazole 40 mg.
Contains no antimicrobial agent.

Use in one patient on one occasion only.
For IV use.

Directions for use: Refer to package insert.

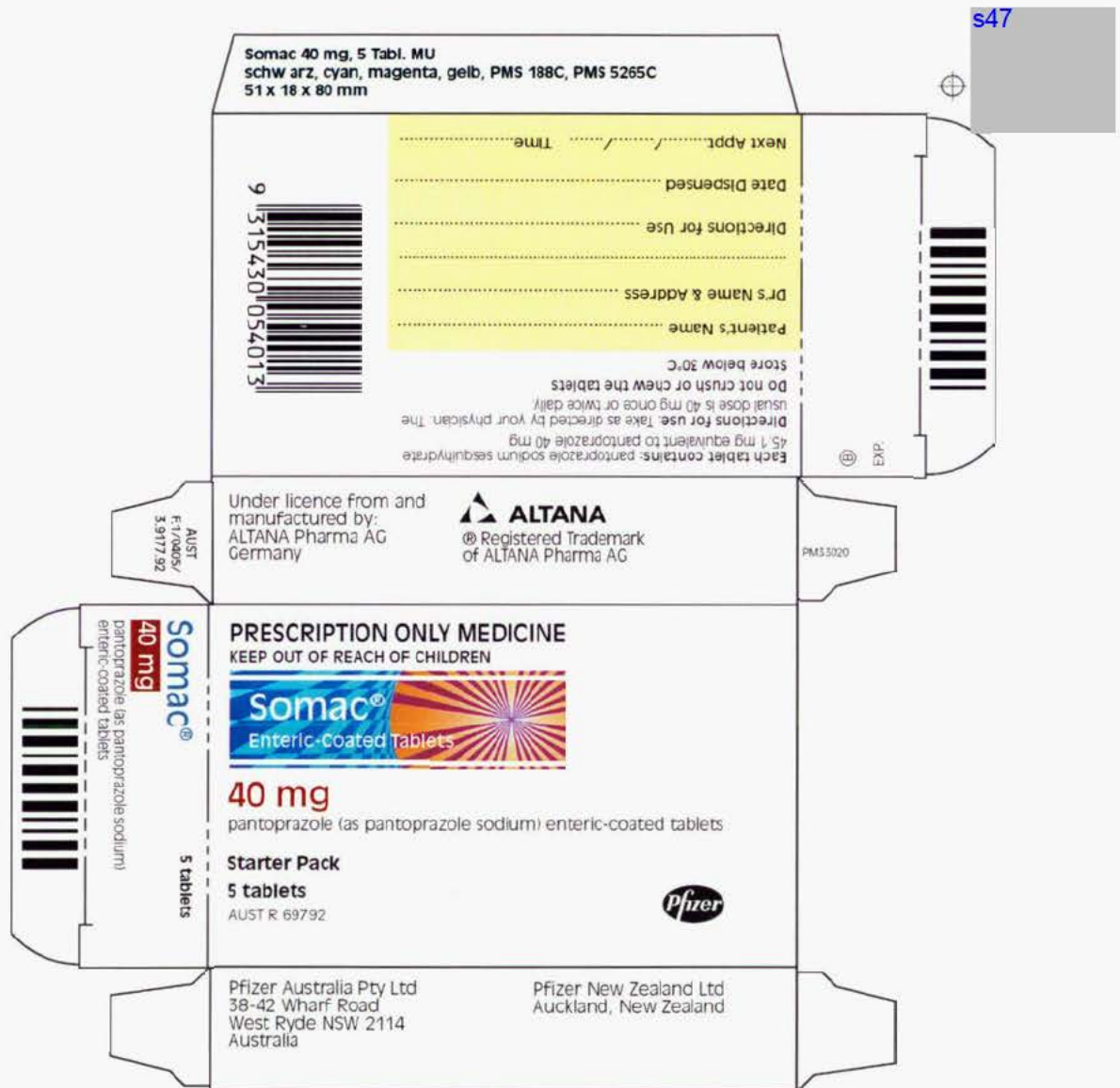
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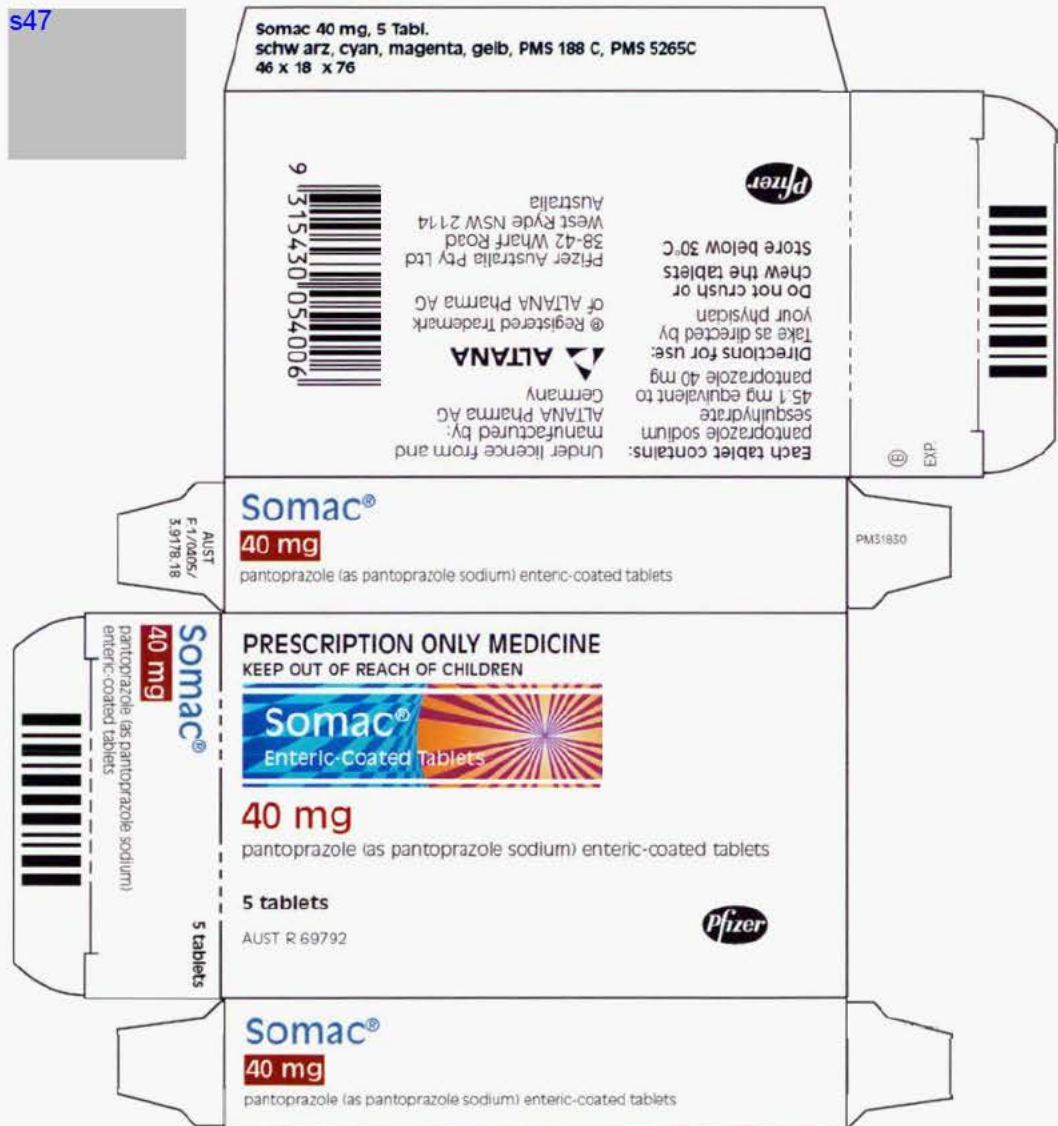
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PS Somac 40 mg 5T_AUST_V01 23.08.2006 11:47 Uhr Seite 1



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V03 73 x 18 x 117 mm

Place label here

Directions for use:
Take as directed by Physician. Do not crush or chew the tablets.
Consumer Medicine Information available at www.takeda.com/en-au
Store below 30° C.
SOMAC® is a registered trademark of Takeda GmbH

®
EXP.:

Somac® 40 mg
pantoprazole 40 mg
30 enteric-coated tablets



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xxxx/
xxxxxx
Code:
xxxx

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN



Somac®
pantoprazole 40 mg

40 mg

Each enteric-coated tablet contains:
pantoprazole sodium sesquihydrate 45.1 mg equivalent
to pantoprazole 40 mg

30 enteric-coated tablets

AUST R 69792



Somac® 40 mg
pantoprazole 40 mg
30 enteric-coated tablets

Takeda Pharmaceuticals Australia Pty Ltd
Sydney, Australia
www.takeda.com/en-au



V03 73 x 18 x 117 mm

Place label here

Directions for use:
Take as directed by Physician. Do not crush or chew the tablets.
Consumer Medicine Information available at www.takeda.com/en-au
Store below 30° C.
SOMAC® is a registered trademark of Takeda GmbH



Somac® 40 mg
pantoprazole 40 mg
30 enteric-coated tablets



9 3 3 5 3 1 1 0 0 0 2 2 9



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xxxxxx
Code:
xxxx

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN



Somac®
pantoprazole 40 mg

40 mg

Each enteric-coated tablet contains:
pantoprazole sodium sesquihydrate 45.1 mg equivalent
to pantoprazole 40 mg

30 enteric-coated tablets

AUST R 69792



Somac® 40 mg
pantoprazole 40 mg
30 enteric-coated tablets



Takeda Pharmaceuticals Australia Pty Ltd
Sydney, Australia
www.takeda.com/en-au









F1/01.2012

73 x 18 x 117

Place label here

® Registered trademark of Takeda GmbH

Directions for use:
Take as directed by Physician. Do not crush or chew the tablets.
Store below 30° C.
Contains sorbates.

EXP.:
®AUS F2/
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6083009
Code:
1655

Somac® 40 mg
pantoprazole 40 mg
30 enteric-coated tablets



PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN



Somac®
pantoprazole 40 mg

40 mg

Each enteric-coated tablet contains:
pantoprazole sodium sesquihydrate 45.1 mg equivalent
to pantoprazole 40 mg

30 enteric-coated tablets

AUST R 69792

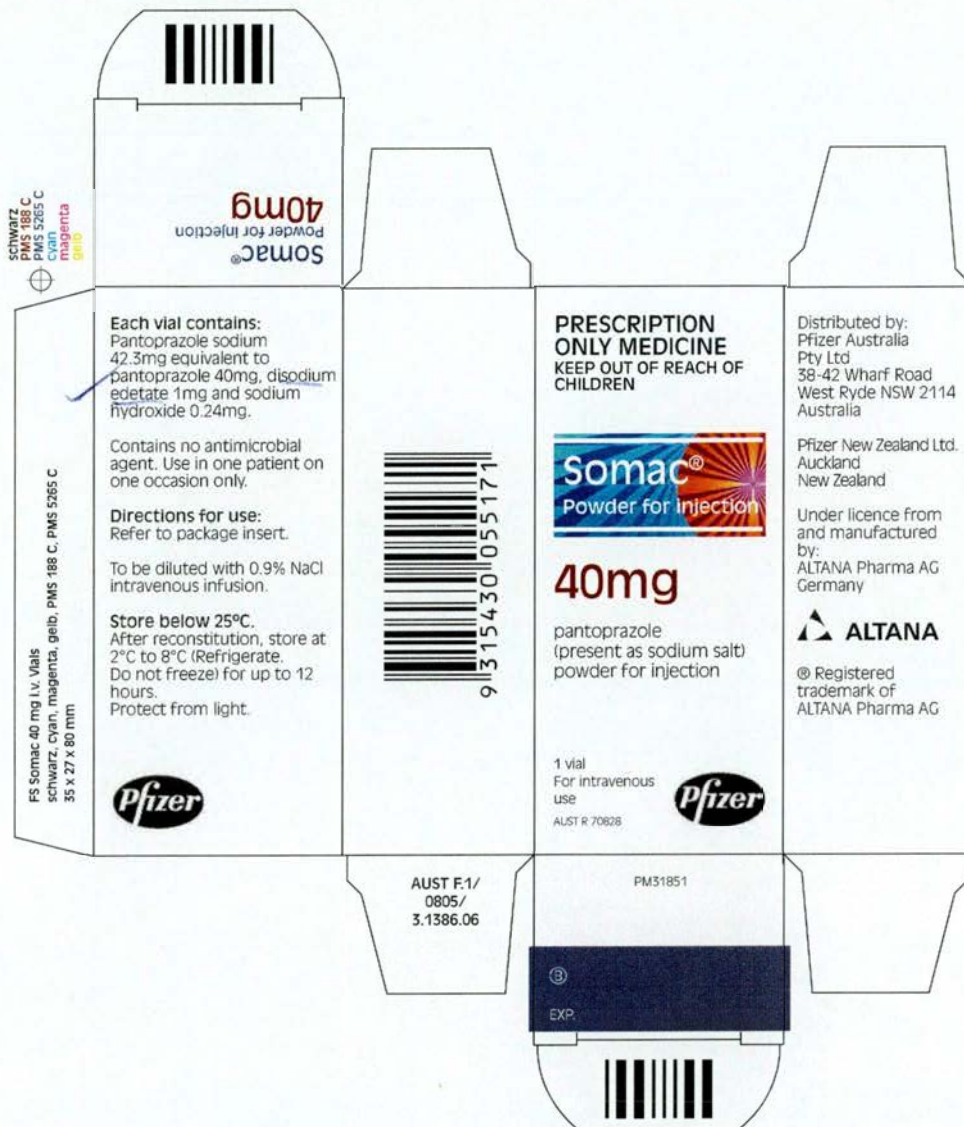


Somac® 40 mg
pantoprazole 40 mg
30 enteric-coated tablets

Distributed in Australia by:
Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000

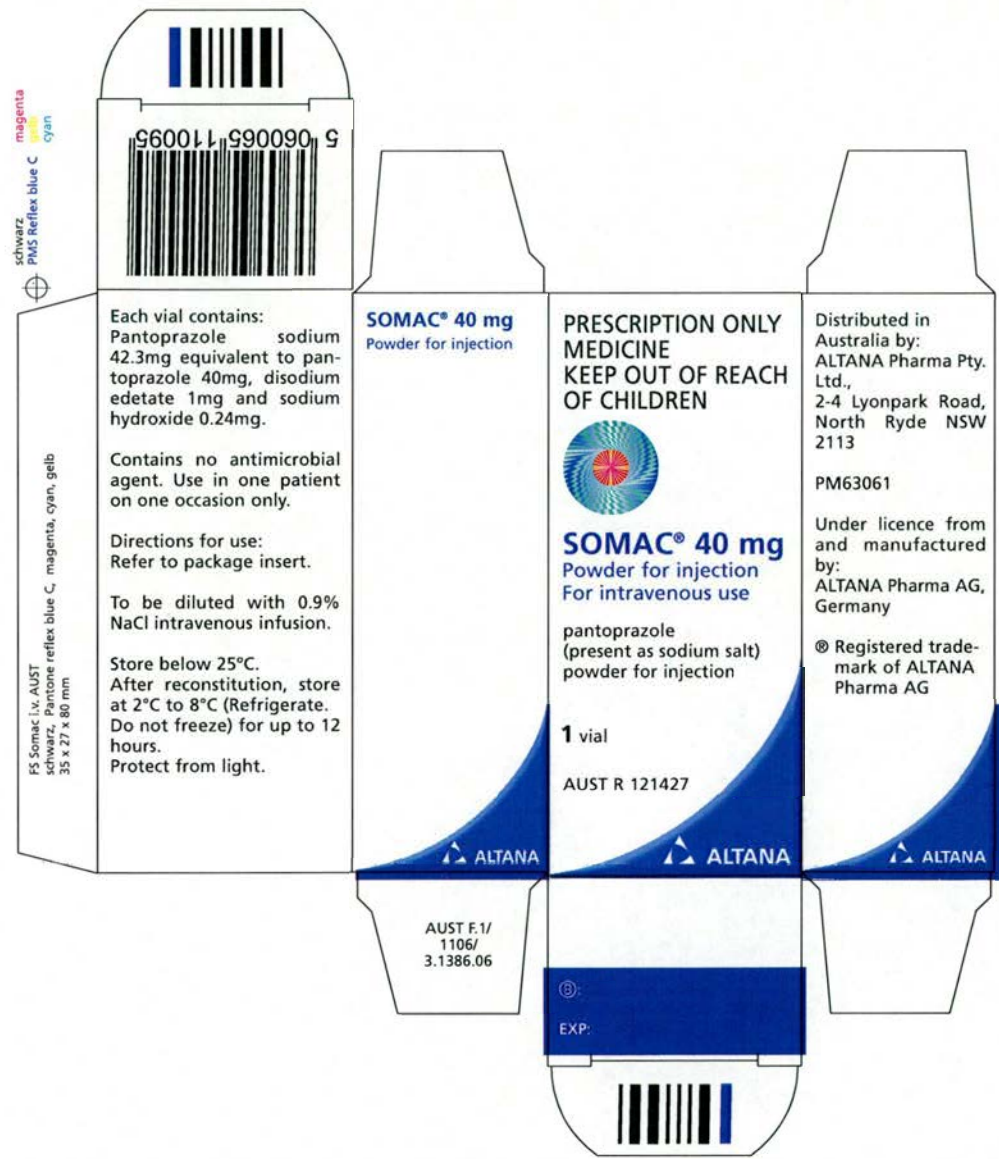


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See vial label
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ET Somac iv AUST_V06 05.12.2006 8:57 Uhr Seite 1

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Somac® 40 mg Powder for injection For IV use
pantoprazole (present as sodium salt)
Each vial contains: Pantoprazole sodium equivalent to
pantoprazole 40 mg. Contains no antimicrobial agent.
Use in one patient on one occasion only. To be diluted
with 0.9% NaCl IV infusion. Directions for use: Refer to
package insert. Store below 25°C. After reconstitution,
store at 2°C to 8°C for up to 12 hours. Protect from light.
Distributed in Australia by: ALIANA Pharma Pty. Ltd., 2-4
Lyonspark Road, North Ryde NSW 2113.
AUST R 121427, PM63061

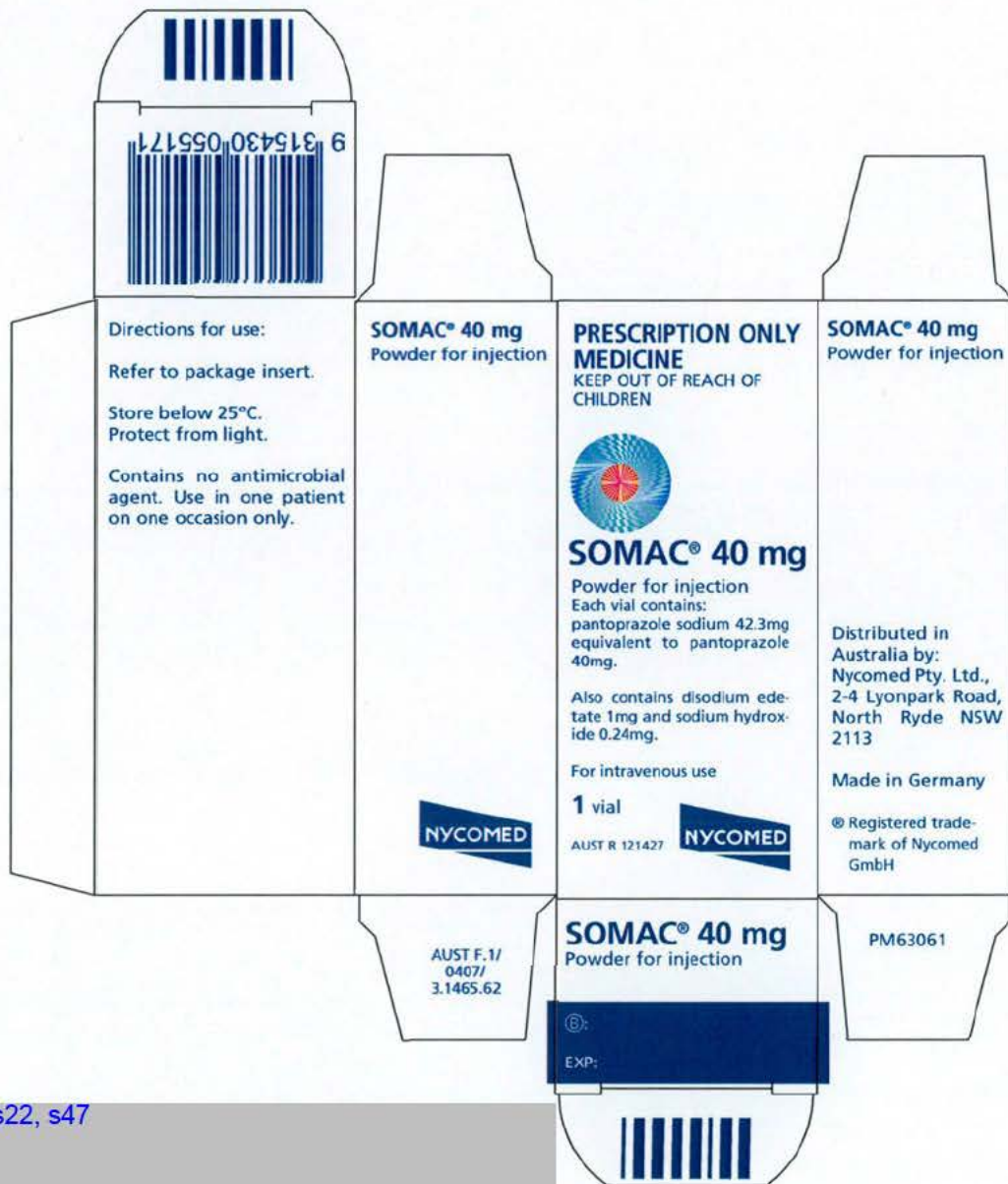
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schwarz
PMS Reflex Blue
65 x 30 mm

schwarz
PMS Reflex Blue



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PRESCRIPTION ONLY MEDICINE**KEEP OUT OF REACH OF CHILDREN**

Somac® 40 mg

Powder for injection

Each vial contains:
Pantoprazole sodium
equivalent to panto-
prazole 40 mg.Contains no antimicrobial
agent. Use in one patient
on one occasion only. For
IV use.Directions for use: Refer
to package insert.**NYCOMED**

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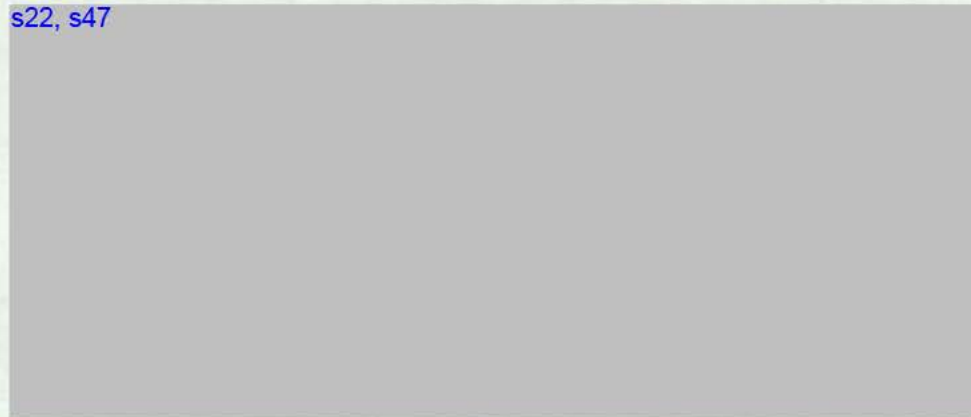
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PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Somac® 40 mg

pantoprazole
Powder for injection

Each vial contains:
pantoprazole sodium
equivalent to
pantoprazole 40 mg

Contains no antimicrobial
agent. Use in one patient
on one occasion only.
For IV use
Directions for use:
Refer to package insert



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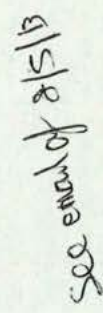


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PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

enteric-coated tablets
pantoprazole (as sodium sesquihydrate)

Each tablet contains:
pantoprazole sodium sesquihydrate 45.1 mg
equivalent to pantoprazole 40 mg

Directions for use:
Take as directed by your physician
Do not crush or chew the tablets
Store below 30°C

Distributed in Australia by:
Nycomed Pty. Ltd.
2-4 Lyonpark Road, North Ryde, NSW 2113

Made in Germany
® Registered trademark of Nycomed GmbH



AUST F. 1/0407/3.9385.73

Somac® 40 mg



enteric-coated tablets
pantoprazole (as sodium sesquihydrate)

AUST R 69792
5 enteric-coated tablets

Somac® 40 mg

NYCOMED

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WT Somac 40 mg 5T AUST
CMYK, PMS Reflex blue C, laseraktiv
74x60,5x5,2 mm

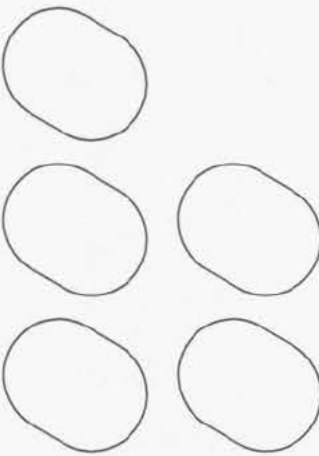
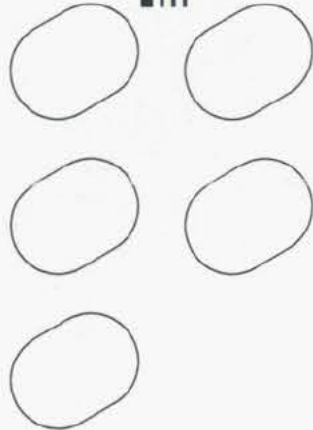
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

enteric-coated tablets
pantoprazole (as sodium sesquihydrate)

Each tablet contains:
pantoprazole sodium sesquihydrate 22.6 mg
equivalent to pantoprazole 20 mg
Directions for use:
Take as directed by your physician
Do not crush or chew the tablets
Store below 30°C
AUST R 69792

Distributed in Australia by:
ALTANA Pharma Pty. Ltd.
2-4 Lyonpark Road, North Ryde, NSW 2113

Under licence from and manufactured by:
ALTANA Pharma AG, Germany



AUST F.1/0506/3.9280.58

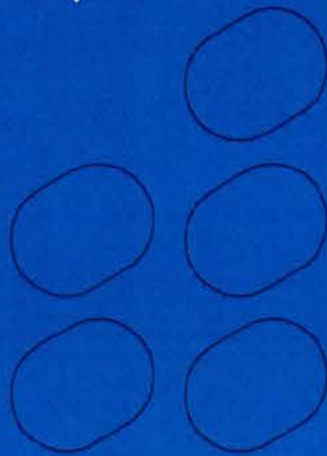
PMS Reflex blue C
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Magenta
gelb
schwarz
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ALTANA

 **Somac® 40 mg**
Pantoprazole

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EXP.

ALTANA



enteric-coated tablets
pantoprazole (as sodium sesquihydrate)

Somac® 40 mg



5 tablets