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)
        - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
        - Reflux oesophagitis
    - Gastrointestinal lesions refractory to H_2 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
    - Clarithomycin 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 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 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 B_{12} absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B_{12}) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} 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 B_{12}) 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)).

Pemetrexed

Concomitant administration of proton pump inhibitors (PPIs) with pemetrexed may increase pemetrexed-related toxicity. Caution should be taken when these medicinal products are co-administered.

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 B_{12} 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 foetuses 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: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥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

Not known: drug fever

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 (³ 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 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.

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 ---------- PCM-P 80/1000/1000-40	7/7/7-7 7/7/7-7	150 147	DU (297)	90.0 % 89.8 %
BGSA010	Single Blind Randomised	PAC 80/2000/1000 ---------- PAC 80/2000/1000	14/7/7 14/14/14	33 34	DU (67)	78.8% 91.2%
BF005	Double Blind Randomised	PAC 80/2000/1000 ---------- PAC 40/2000/1000	7/7/7 7/7/7	96 96	NUD (192)	75.0% 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 %

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)
		---------- 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 ---------- PC-P 80/1500-40	7/7/7/-21 14/14/-14	136 141	DU (277)	89.0 % 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

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

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 ± 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 (δ23%) 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

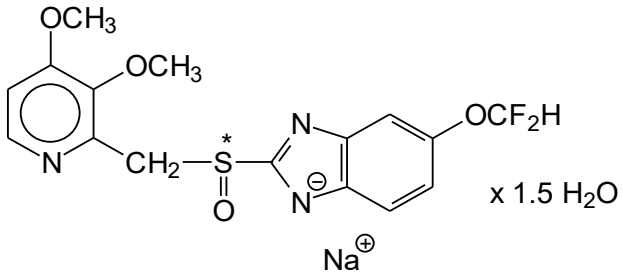
Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

Chemical name (CAS): Sodium-[5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide sesquihydrate

Molecular formula: $C_{16}\ H_{14}\ F_2\ N_3\ NaO_4S.1½\ H_20$

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 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

8 July 1999

10 DATE OF REVISION

07 July 2026

Summary table of changes

Section changed	Summary of new information
4.8	Addition of adverse drug reaction ‘Drug fever’