AUSTRALIAN PRODUCT INFORMATION

SALPRAZ

Pantoprazole (as pantoprazole sodium sesquihydrate) tablets

1 NAME OF THE MEDICINE

Pantoprazole (as pantoprazole sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SALPRAZ 20 mg enteric coated tablets contain 22.560 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole.

SALPRAZ 40 mg enteric coated tablets contain 45.120 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

Excipients with known effects: Salpraz also contains traces of soya bean products.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Salpraz tablets are yellow coloured, oval, biconvex enteric coated tablets plain on both the sides.

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 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

SALPRAZ tablets should not be chewed or crushed but swallowed whole with a little water.

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) SALPRAZ 40 mg twice daily plus amoxicillin 1000 mg (2 x 500 mg) twice daily plus clarithromycin 500 mg twice daily
b) SALPRAZ 40 mg twice daily plus metronidazole 400 mg in the morning and 600 mg at night plus clarithromycin 500 mg twice daily
c) SALPRAZ 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) SALPRAZ 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 SALPRAZ 40 mg should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with SALPRAZ 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. SALPRAZ 40 mg (1 tablet) 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. SALPRAZ 40 mg (1 tablet) 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. SALPRAZ 40 mg (1 tablet) 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 SALPRAZ 40 mg tablets 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 SALPRAZ 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 SALPRAZ 20 mg tablets daily, further investigation is recommended, for example endoscopy.

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

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 SALPRAZ 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)).

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 SALPRAZ 20 mg who do not respond after 4 weeks should be investigated.

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 Hepatic Impairment

Refer to Section 4.2 Dose and Method of Administration – Impaired Hepatic Function.

Use in Renal Impairment

Refer to Section 4.2 Dose and Method of Administration – Impaired Renal Function.

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 ethinylestradiol). 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 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.

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)

SALPRAZ 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

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 and 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: 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, 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 (≥ 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%)
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 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 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 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*.

Clinical Trials

No data available.

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 Cmax 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.

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 (δ 23%) 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 population – hepatic impairment

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.

Special population – renal impairment

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.

Special population – elderly

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

Special population – 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.

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

In addition to pantoprazole sodium, the tablets also contain Sodium Carbonate, Calcium stearate, Mannitol, Povidone K-30, Crospovidone, Hypromellose, Macrogol 6000, Methacrylic acid- ethyl acrylate copolymer (1:1), Triethyl citrate, Purified Talc, Opadry AMB Aqueous Moisture Barrier Coating System 80W52172 Yellow (ID- 106688), Carnauba Wax (Powder) and Purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Al/Al blister packs

Pack sizes:

20 mg tablets are available in blisters of 30s.

40 mg tablets are available in blisters of 30s.

Some strengths, pack sizes and/or pack types may not be marketed.

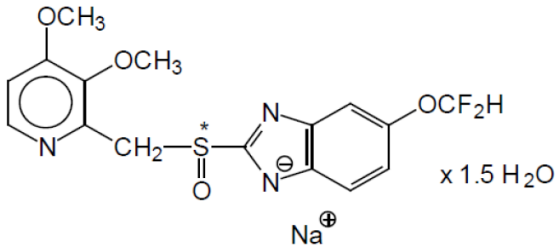
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder. 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-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)

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

22 May 2020

10 DATE OF REVISION

8 September 2020

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

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