Australian Product Information -
SOZOL (Pantoprazole (as sodium sesquihydrate)) TABLETS

1 NAME OF THE MEDICINE

Pantoprazole sodium (as pantoprazole sodium sesquihydrate).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SOZOL 20 mg enteric coated tablet contains 22.7 mg pantoprazole sodium sesquihydrate equivalent to 20 mg of pantoprazole.

Each SOZOL 40 mg enteric coated tablet contains 45.4 mg of pantoprazole sodium sesquihydrate equivalent to 40 mg of pantoprazole.

Excipients of known effect: Contains soya bean products as a component of the OPADRY AMB Coating System (Proprietary Ingredient No. 106688).

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

3 PHARMACEUTICAL FORM

SOZOL is available as 20 mg (yellow to pale yellow, oval shaped, plain on both sides) and 40 mg (yellow to pale yellow, oval shaped, plain on both sides) biconvex, enteric-coated tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. For symptomatic improvement and healing of the following gastrointestinal diseases which require a reduction in acid secretion:

- duodenal ulcer
- gastric ulcer
- gastro-oesophageal reflux disease (GORD):
    I. symptomatic GORD. The treatment of heartburn and other symptoms with GORD
    II. 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. 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults:

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

Duodenal ulcer: SOZOL 40 mg (one tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

Gastric ulcer: SOZOL 40 mg (one tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes four weeks. If a four-week period of treatment is not sufficient, healing will usually be achieved in a further four weeks.

Lesions refractory to H2-receptor antagonists: SOZOL 40 mg (one tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes four weeks. If a four-week period of treatment is not sufficient, healing is achieved in the majority of patients in a further four 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 SOZOL 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.

Gastroesphageal reflux disease (GORD):

Symptomatic GORD (treatment of symptomatic reflux): The recommended dosage is one SOZOL 20 mg tablet per day. If symptom control has not been achieved after four weeks treatment with SOZOL 20 mg tablets daily, further investigation is recommended, for example, endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one SOZOL 20 or 40 mg tablet/day. A four-week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further four weeks. This dosage may be increased up to pantoprazole 80 mg/day.

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

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with nonselective NSAIDs in increased risk patients with a need for continuous nonselective NSAID treatment: The recommended oral dosage is one SOZOL 20 mg tablet per day.

Infants and children:

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

Use in the elderly:

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

Renal insufficiency:

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

Hepatic insufficiency:

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.

Monitoring advice:

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

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 B12) due to hypochlorhydria 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 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 SOZOL 20 mg for prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective NSAIDs should be restricted to patients who require continued non-selective NSAID treatment and have an increased risk of developing gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (> 65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (see section 4.8 Adverse Effects (Undesirable Effects)). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Subacute Cutaneous Lupus Erythematosus (SCLE)
Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping the product.

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

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

Hypomagnesaemia
Hypomagnesaemia has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, arrhythmia, and seizure. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (**see section 4.8 Adverse Effects (Undesirable Effects)**).

General Toxicity:

Gastrointestinal system:

Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; 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 dysplasic 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 of up to 15 mg/kg/day for 4 weeks.

Monitoring

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

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

Use in hepatic impairment: **See section 4.2 Dose and method of administration - Hepatic insufficiency and section 5.2 Pharmacokinetic properties – Special population.**

Use in renal impairment: **See section 4.2 Dose and method of administration - Renal insufficiency and section 5.2 Pharmacokinetic properties – Special population.**

Use in the elderly: See section 4.2 Dose and method of administration - Use in elderly, 4.4 Special warnings and Precautions for use – Influence on Vitamin B12 and section 5.2 Pharmacokinetic properties – Special population.

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 ethinyloestradiol). 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 crossover pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxycillin 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 coadministration 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 coadministered 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 studies in rats, dose dependent toxic effects were observed on foetuses and pups: increased prenatal and postnatal deaths 450 mg/kg/day (AUC exposure approximately 60-times the clinical exposure of the 40 mg oral dose), reduced fetal weight (greater than or equal to 150 mg/kg/day) and delayed skeletal ossification and reduced pup growth (greater than or equal to 15 mg/kg/day). For the latter, a no effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the foetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy unless the benefit clearly outweighs the potential risk to the 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 group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines, however, adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8 Adverse Effects (Undesirable Effects)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment are 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

Frequency not known: 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 reports of tinnitus.

Immune system disorders:

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

Hepatobiliary disorders:

Uncommon: increased liver enzymes

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.

Metabolic and nutritional disorders:

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

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (**see Section 4.4 Special Warnings Precautions for Use**).

Musculoskeletal and connective tissue disorders:

Rare: myalgia and arthralgia.

Very rare: pain including skeletal pain.

Not known: fracture of wrist, hip and spine

Renal and urinary disorders:

Very rare: tubulointerstitial nephritis (TIN) (with possible progression to renal failure).

Platelet, bleeding, clotting disorders:

Very rare: increased coagulation time.

Psychiatric disorders:

Uncommon: sleep disorders

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

Very rare reports of 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 and skin 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: disturbances in vision (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%)
Adverse event	**PBMT** (n=422)	**BMT** (n=600)	**PAC** (n= 368)
Pruritus ani	---	7 (1.2%)	---

Central & peripheral nervous system disorders			
Headache	49 (11.6%)	65 (10.8%)	38 (10.3%)
Dizziness	30 (7.1%)	38 (6.3%)	25 (6.8%)
Special senses other, disorders			
Taste perversion	45 (10.7%)	65 (10.8%)	67 (18.2%)
Psychiatric disorders			
Anorexia	11 (2.6%)	19 (3.2%)	17 (4.6%)
Somnolence	---	8 (1.3%)	---
Depression	---	---	4 (1.1%)
Gastrointestinal disorders			
Diarrhoea	49 (11.6%)	56 (9.3%)	37 (10.1%)
Nausea	38 (9.0%)	58 (9.7%)	34 (9.2%)
Abdominal pain	27 (6.4%)	37 (6.2%)	24 (6.5%)
Vomiting	7 (1.7%)	12 (2.0%)	8 (2.2%)
Faeces discoloured	7 (1.7%)	18 (3.0%)	---
Tongue discolouration	10 (2.4%)	11 (1.8%)	---
Mouth dry	---	13 (2.2%)	4 (1.1%)
Constipation	---	---	8 (2.2%)
Dyspepsia	---	6 (1.0%)	---
Respiratory system disorders			
Pharyngitis	8 (1.9%)	9 (1.5%)	7 (1.9%)
Body as a whole - general disorders			
Influenza-like symptoms	15 (3.6%)	12 (2.0%)	14 (3.8%)
Chest pain	5 (1.2%)	---	4 (1.1%)
Resistance mechanism disorders		---	
Moniliasis	6 (1.4%)		5 (1.4%)

---- Events reported by < 1%

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

	Overall Children		
Patients (N)	250		
	No of AE	**No of patients with AE**	**% patients with AE**

Headache	201	66	26.4
Nasopharyngitis	67	34	13.6
Pharyngolaryngeal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

Reporting suspected adverse effects:

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

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

As pantoprazole is extensively protein bound, it is not readily dialyzable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

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

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

Clinical trials

Treatment of symptomatic reflux (GORD): The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo-controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled in 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 three months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in the table below.

Efficacy of pantoprazole in treatment of symptomatic GORD

	1 WEEK			**2 WEEKS**		
	Pantoprazole 20 mg	**Placebo**	**p**	**Pantoprazole 20 mg**	**Placebo**	**p**
Per protocol n = 211 (week 1) n = 204 (week 2)	69%	30%	P<0.001	80%	46%	p<0.001
Intention to treat n = 219	67%	32%	P<0.001	74%	43%	p<0.001

Acute treatment of mild reflux oesophagitis: In two randomised, double blind, multicentre studies (BGSA006 and FK3034) 410 patients with mild gastroesophageal reflux disease (GORO) (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 compared to ranitidine after four and eight weeks is shown in Table below. The difference in healing rates was statistically significant at all time points in the intention to treat and per protocol patient groups.

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 to 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. The results for the incidence of relapse in patients with data from at least one follow-up visit are outlined in the table below.

Incidence of relapse[1] (%) of reflux oesophagitis[2] in controlled trials of 12 months duration (evaluable patients)

Trial	Pantoprazole 20mg/day	Pantoprazole 40mg/day	Ranitidine 150mg/day	Difference (90%CI)
FK 3028	25%	22%	-	2.7%
	(n=221)	(n=212)		(-5, 10)
FK 3033	28%	19%	-	9%
	(n=203)	(n=193)		(1, 17)
BGSA008	35%	-	72%	37%
	(n=75)	-	(n=40)	23,52)

1 endoscopically confirmed

2 patients were enrolled in the study with Savary-Miller stage 2 to 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 the 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**). 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 nonselective 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 of developing gastrointestinal lesions.

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

Study 205/2000: A total of 515 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n = 257) or misoprostol 200 microgram twice daily (n = 258). Efficacy of pantoprazole 20 mg is shown in the table below.

	Time Interval	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 microgram twice daily with regard to 'therapeutic failure' and to 'endoscopic failure'. Reflux oesophagitis was included as an efficacy endpoint 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.

	Time interval (months)	Pantoprazole 20 mg	Pantoprazole 40mg	Omeprazole 20mg
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, pantoprazole 20 mg, pantoprazole 40 mg and omeprazole 20 mg, were proven to be of equivalent and high efficacy

5.2 PHARMACOKINETIC PROPERTIES

Absorption:

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h. In the fasted state, it was found that the C_{max} of SOZOL 40 mg tablets was 3.6 microgram/mL. Terminal half-life is approximately 1 h.

Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80 mg) after both oral and intravenous (IV) administration.

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability.

Distribution:

The serum protein binding of pantoprazole is approximately 98%. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg.

Metabolism*:*

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4.

There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤ 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 populations:

In patients with liver cirrhosis given a single 40mg 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 20mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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

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

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 has been detected.

Pantoprazole was found to be negative in the following studies*: in vivo* chromosome aberration assay in rat and bone marrow (126E/95), mouse lymphoma test (222E/95) and a gene mutation test in Chinese hamster ovary cells (*in vitro*) (188E/95). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710 mg/kg) (89E/96). 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 – 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 25mg/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 doses (5, 15 and 50 mg/kg, 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

- mannitol
- sodium carbonate
- sodium starch glycollate
- crospovidone
- colloidal anhydrous silica
- calcium stearate
- hypromellose
- macrogol 6000
- sodium hydroxide
- EUDRAGIT L30-D55 (Proprietary Ingredient No. 3700)
- OPADRY AMB Aqueous Moisture Barrier Coating System 80W52172 Yellow (Proprietary Ingredient No. 106688)

SOZOL tablets are gluten free.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The blister is made of Al/Al.

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

SOZOL 40 mg are available in blister packs of 30 tablets.

Other pack sizes currently not marketed are 5, 14, 15, 28, 50, 56, 60, 100 and 140 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

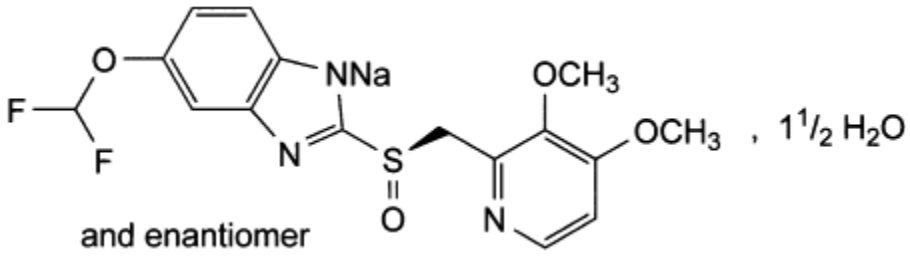
Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. It is a white to off white crystalline powder. Freely soluble in water and in ethanol (96 per cent), practically insoluble in hexane. Solubility is low at neutral pH and increases with increasing pH.

Chemical name: Sodium 5-(difluoromethoxy)-2-[(RS)-[(3,4-Dimethoxy pyridin-2-yl)methyl]sulphinyl]benzimidazol-1-ide sesquihydrate

Molecular formula: $C_{16}H_{14}F_2N_3Na0_4S$ 1½ H_20

Molecular weight: 432.4 (Sodium salt x 1.5 H_2O)

Chemical structure



CAS number

Cas No.: 164579-32-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

27th February 2012

10 DATE OF REVISION

25 November 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4 & 4.8	Addition of Severe Cutaneous Adverse Reactions (section 4.4), addition of acute generalised exanthematous pustulosis (section 4.8)