AUSTRALIAN PRODUCT INFORMATION

SALPRAZ® HEARTBURN RELIEF

(pantoprazole (as sodium sesquihydrate)) tablets (reformulation 2)

1 NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SALPRAZ HEARTBURN RELIEF enteric coated tablet contains 22.6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg of pantoprazole.

Excipients with known effects: trace quantities of soya bean products.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

SALPRAZ HEARTBURN RELIEF are yellow, oval shaped, plain on both sides, biconvex, enteric-coated tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Heartburn and Gastro-Oesophageal Reflux disease

SALPRAZ HEARTBURN RELIEF is used for the relief of symptoms of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults:

SALPRAZ HEARTBURN RELIEF is indicated for use in adults 18 years of age and over. The recommended dosage is one SALPRAZ HEARTBURN RELIEF tablet per day for at least 7 days, and up to 14 days. If symptoms relief has not been achieved after two weeks of continuous treatment with one SALPRAZ HEARTBURN RELIEF tablet per day, patients should be referred to their doctor. SALPRAZ HEARTBURN RELIEF tablets should not be chewed or crushed but swallowed whole with a little water.

Children and adolescents < 18 years:

There are no data currently available on the use of pantoprazole in children. SALPRAZ HEARTBURN RELIEF is not recommended for use in children and adolescents under 18 years of age.

Use in hepatic impairment:

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Section 4.3 CONTRAINDICATIONS). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

Use in renal impairment:

No dose adjustment is required in patients with impaired renal function.

Use in the elderly:

No dose adjustment is necessary in elderly patients.

4.3 CONTRAINDICATIONS

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

Pantoprazole, like other proton pump inhibitors, should not be co-administered with HIV protease inhibitors, such as atazanavir or nelfinavir (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be referred to their doctor if:

- They have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded. They have had to take other medication for ingestion or heartburn continuously for four or more weeks in order to control their symptoms.

- They are being treated for symptomatic GORD and require SALPRAZ HEARTBURN RELIEF for more than 14 days.

- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or

- They have any other significant medical condition.

Clostridium difficile:

Proton pump inhibitor (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 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 hypochlorhydria 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 and in patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions or if respective clinical symptoms are observed. Rare cases of cyanocobalamin deficiency following acid-blocking therapy have been reported.

Bone fracture

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

Acute Interstitial Nephritis

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

Hypomagnesaemia

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

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 generalised 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.

Pemetrexed

Concomitant administration of 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; 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 (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Monitoring

Patients being treated for symptomatic GORD with SALPRAZ HEARTBURN RELIEF who do not respond to treatment after two weeks should consult their doctor.

Use in hepatic impairment

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Section 4.3 CONTRAINDICATIONS). No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

Use in renal impairment

No dose adjustment is required in patients with impaired renal function.

Use in the elderly

No dose adjustment is necessary in elderly patients. See Sections 4.2 DOSE AND METHOD OF ADMINSTRATION; 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.

Effects on laboratory use

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism.

In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and the combined low dose oral contraceptive 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 crossover pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

Coumarin anticoagulants (phenprocoumon or warfarin)

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) and prothrombin time have been reported during concomitant treatment in the postmarketing period. 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.

Methotrexate

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

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.

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.

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 dose) 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 fetuses and pups: increased prenatal and postnatal deaths (450 mg/kg/day), 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 fetus are increased shortly before birth regardless of the route of administration.

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

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole has no or negligible influence on the ability to drive and use machines. Pantoprazole does not exert its pharmacological action centrally, therefore it is not expected to adversely affect the ability to drive or use machines. However, adverse drug reactions such as dizziness and visual disturbances may occur (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥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, malaise, asthenia and increased sweating

Rare: fever and 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 sense of smell and taste

Gastrointestinal system disorders

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

Rare: rectal disorder and colonic polyp

Very rare: faecal discolouration and increased saliva

Not known: flatulence, severe eructation, 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 (transaminases, gamma GT)

Rare: bilirubin increased

Very rare: hepatocellular failure, cholestatic hepatitis and jaundice

Not known: hepatocellular injury

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

Metabolism and nutrition disorders

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

Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia (hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia

Very rare: pain including skeletal pain

Not known: fracture of wrist, hip and spine

Renal and urinary disorders

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

Platelet, bleeding, clotting disorders

Very rare: increased coagulation time

Blood and lymphatic system disorders

Rare: anaemia, agranulocytosis

Very rare: leukopenia, thrombocytopenia, pancytopenia

Psychiatric disorders

Uncommon: sleep disorders

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

Very rare: anxiety

Resistance mechanism disorders

Rare: sepsis

Respiratory system disorders

Very rare: dyspnoea

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/ eruption

Rare: angioedema and urticaria

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

Not known: subacute cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis

Reproductive system and breast disorders

Rare: gynaecomastia

Eye disorders

Uncommon: disturbances in vision (blurred vision)

Very rare: conjunctivitis

Reporting suspected adverse effects

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

4.9 OVERDOSE

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

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 dialysable. As in any case of overdosage, treatment should be symptomatic and supportive measures should be utilised.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic 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

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. 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 metabolisers 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 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 1.1h 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 Cmax 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. No distinct DNA-adduct has been detected.

Mutagenesis

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

Carcinogenity

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 development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day (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). 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

SALPRAZ HEARTBURN RELIEF tablets contain Sodium carbonate, Calcium stearate, Mannitol, Povidone, 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 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 30^0C.

6.5 NATURE AND CONTENTS OF CONTAINER

SALPRAZ HEARTBURN RELIEF tablets are available in Al/Al aluminium blister packs of 7's and 14's. Not all pack sizes may be marketed.

Australian Register of Therapeutic Goods (ARTG)

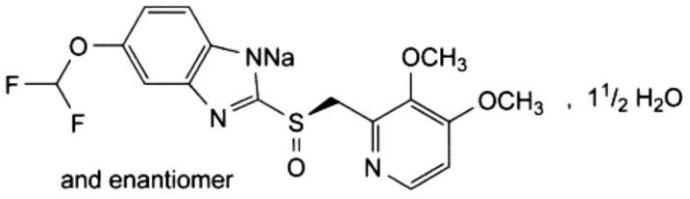
AUST R 348230 – SALPRAZ HEARTBURN RELIEF pantoprazole (as sodium sesquihydrate) 20 mg enteric-coated tablet blister pack (reformulation 2)

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:



CAS Number: 164579-32-2

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_20)

Pantoprazole sodium sesquihydrate 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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

7's pack; S2 (Pharmacy Medicine)

14's pack; S3 (Pharmacist Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

12/11/2020

10 DATE OF REVISION

29/06/2026

Summary Table of Changes

Section changed	Summary of new information
All	Minor editorial changes
4.4	Addition of warning related to Drug Interaction with Pemetrexed

SALPRAZ® is a Viatris company trade mark

SALPRAZ HEARTBURN RELIEF_pi\Jun26/00