AUSTRALIAN PRODUCT INFORMATION PANTOPRAZOLE APOTEX TABLETS (PANTOPRAZOLE SODIUM SESQUIHYDRATE)

1 NAME OF THE MEDICINE

Pantoprazole sodium sesquihydrate.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

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

Each enteric coated tablet contains the active ingredient pantoprazole (as sodium sesquihydrate). In addition, each enteric coated tablet contains the following inactive ingredients: mannitol, sodium carbonate, sodium starch glycollate, crospovidone, colloidal anhydrous silica, calcium stearate, hypromellose, macrogol 6000, sodium hydroxide, Eudragit L30-D55 and Opadry AMB Aqueous Moisture Barrier Coating System 80W52172 Yellow.

PANTOPRAZOLE APOTEX Tablets 20 mg (AUST R 213715) and PANTOPRAZOLE APOTEX Tablets 40 mg (AUST R 213716) are yellow to pale yellow, oval, biconvex enteric-coated tablets, plain on both sides.

The enteric coated tablets are intended for oral administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

- Duodenal ulcer.
- Gastric ulcer.
- Gastro-oesophageal reflux disease (GORD).
  - Symptomatic GORD: the treatment of heartburn and other symptoms associated with GORD.
  - Reflux oesophagitis.
- Gastrointestinal lesions refractory to H_2-blockers.
- Zollinger-Ellison syndrome.

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

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

III. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with nonselective NSAIDs in increased risk patients with a need for continuous nonselective NSAID treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Duodenal Ulcer
Pantoprazole 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
Pantoprazole 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 H_2-Receptor Antagonists
Pantoprazole 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 pantoprazole 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.

Gastroesophageal Reflux Disease (GORD)

Symptomatic Gastroesophageal Reflux Disease (Treatment of Symptomatic Reflux)
The recommended dosage is one pantoprazole 20 mg tablet/day. If symptom control has not been achieved after four weeks treatment with pantoprazole 20 mg tablets daily, further investigation is recommended, for example, endoscopy.

Treatment of Reflux Oesophagitis
The recommended oral dosage is one pantoprazole 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 pantoprazole 20 or 40 mg tablet/day is recommended, dependent upon patient response.

Prevention of Gastroduodenal Lesions and Dyspeptic Symptoms Associated with Non-Selective NSAIDs in Increased Risk Patients with a Need for Continuous Non-Selective NSAID Treatment
The recommended oral dosage is one pantoprazole 20 mg tablet/day.

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

Use in the Elderly
The usual daily dose of 20 or 40 mg can be given.

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

Impaired Hepatic Function
Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see Section 4.3 Contraindications).

With milder forms of liver disease, the 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.

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 concomitant use with other antibiotics, the product information for the other antibiotics used should be observed.

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

Clostridium difficile

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

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

Pantoprazole, as all acid blocking medicines, may reduce the absorption of cyanocobalamin (vitamin 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) 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 B_{12}) deficiency following acid blocking therapy have been reported.

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

Bone Fracture

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

Acute Interstitial Nephritis

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

Hypomagnesaemia

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

Monitoring

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

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

Use in the elderly

See section 4.2 - Use in the elderly, section 4.4 - Clostridium difficile and section 5.2 - Excretion

Paediatric use

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

Effects on laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours.

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 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 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 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 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 fetuses and pups: increased prenatal 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 foetus are increased shortly before birth regardless of the route of administration.

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

Use in lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day (AUC exposure approximately the clinical exposure of the 40 mg oral dose) or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day (AUC exposure approximately 3-fold the clinical exposure) group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breastfeeding 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). If affected, patients should not drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pantoprazole is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone, or in concomitant use with other antibiotics, in clinical trials and postmarketing 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%; and not known: cannot be estimated from the available data). These include the following:

<u>General Disorders and Administration Site Conditions</u>

Uncommon:	fatigue and malaise, asthenia and increased sweating.
Rare:	fever, peripheral oedema and increased body temperature.
Very rare:	flushing, substernal chest pain and hot flushes.

Cardiovascular Disorders, General
Rare: hypertension.
Very rare: circulatory collapse.

Nervous System Disorders
Uncommon: headache, dizziness.
Rare: taste disorders, metallic taste.
Very rare: reduced movement and speech disorder, changes to the senses of smell and taste.

Gastrointestinal System Disorders
Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort.
Rare: rectal disorder and colonic polyp.
Very rare: faecal discolouration and increased saliva.
Not known: severe eructation.

Hearing and Vestibular Disorders
Very rare: tinnitus.

Immune System Disorders
Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatobiliary System Disorders
Uncommon: liver enzymes increased (transaminases, gamma-GT).
Rare: bilirubin increased.
Very rare: hepatocellular failure, cholestatic hepatitis, jaundice.
Not known: hepatocellular injury.

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

Metabolism and Nutrition Disorders
Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes.
Not known: hyponatraemia, hypomagnesaemia.

Musculoskeletal and Connective Tissue Disorders
Rare: myalgia, arthralgia.
Very rare: pain including skeletal pain.
Not known: fracture of wrist, hip and spine.

Renal and Urinary Disorders
Very rare: interstitial nephritis.

Platelet, Bleeding, Clotting Disorders
Very rare: increased coagulation time.

Psychiatric Disorders
Uncommon: sleep disorders

Rare: depression (and all aggravations), hallucination, disorientation (and all aggravations) and confusion, especially in predisposed patients, as well as the aggravation of these symptoms in the 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

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 used Concomitantly with other Antibiotics

Event	PCM/T* (n=725)	PAC (n=492)	PAM (n=146)
Diarrhoea	4.8	10.0	7.5
Taste bitter	4.0	3.0	0
Nausea	3.7	1.2	1.4
Taste metallic	2.1	0.2	0
Upper abdominal pain	1.9	1.4	0
Headache	1.8	1.8	0
Dizziness	1.4	0.6	0
Tongue pain	1.2	0.8	0
Liver enzymes increased	1.2	0.2	0
Tiredness	1.1	0	0.7
Loose stools	1.0	0.8	0
Oral moniliasis	1.0	0.4	0
Buccal inflammation	1.0	0	0
Exanthemata	0.4	1.2	0.7
Heartburn	0.4	0.4	2.7

Event	PCM/T* (n=725)	PAC (n=492)	PAM (n=146)
Dyspepsia	0.1	0.6	1.4
Rash	0.1	0.6	1.4
At least one of the above	34	29	20

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

Table 2: Adverse Events (≥ 1%) reported in a Clinical Trial comparing Quadruple and Triple Therapies 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 2–16 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
Pharyngolareal pain	58	33	13.2
Nasal congestion	32	14	5.6
Diarrhoea	20	13	5.2
Cough	20	13	5.2

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems and contact Apotex Medical Information enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Symptoms

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

Treatment

Standard detoxification procedures apply.

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 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 H_2-receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

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 non-steroidal anti-inflammatory drug (NSAID) ingestion. 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

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, multicentre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least three months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 3.

Table 3: Efficacy of Pantoprazole 20 mg in the Treatment of Symptomatic Reflux

Data set	1 week			2 weeks		
	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 (GORD) (Savary-Miller stage 1) were treated with either pantoprazole 20 mg once daily before breakfast or ranitidine 300 mg once daily at bedtime. Superiority of pantoprazole 20 mg in terms of healing rates as compared to ranitidine after four and eight weeks is shown in Table 4. The difference in healing rates was statistically significant at all time points in the intention-to-treat and per protocol patient groups.

Table 4: Endoscopic Healing of Stage 1 Oesophagitis (Intention to Treat)

Trial/group	n	% Patients healed	
		4 weeks	8 weeks
BGSA006			
Pantoprazole	101	73.3	83.2
Ranitidine	100	49.0	69.0
Difference		p < 0.05	p < 0.05
FK3034			
Pantoprazole	105	66.7	74.3
Ranitidine	104	52.9	60.6
Difference		p < 0.05	p < 0.05

Maintenance of Healed Reflux Oesophagitis in Patients Previously Treated for Moderate to Severe Reflux Oesophagitis

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

Table 5: Incidence of Relapse[1] (%) of Reflux Oespophagitis[2] in Controlled Trials of 12 months Duration (Evaluable Patients)

Trial	Pantoprazole 20 mg/day	Pantoprazole 40 mg/day	Ranitidine 150 mg/day	Difference (90% CI)
FK 3028	25% (n = 221)	22% (n = 212)	–	2.7% (-5, 10)
FK3033	28% (n = 203)	19% (n=193)	–	9% (1, 17)
BGSA008	35% (n = 75)	–	72% (n = 40)	37% (23, 52)

[1] Endoscopically confirmed

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

Pantoprazole 20 and 40 mg/day doses were therapeutically equivalent based on the predefined 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 one year was 12–15%, at two years was 22–25% and at six years was 40%.

Safety data are available from the 1,584 patients involved in the seven long-term clinical studies. 904 patients have been treated with pantoprazole for at least one year, and 273, 112, 68, 47 and 17 have been treated for at least two, three, four, five and six years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but six were classified as being causally unrelated to pantoprazole (four cases with pantoprazole 40 mg: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus two cases with high dose pantoprazole: anaemia and hypertension) (see Section 4.8 Adverse effects). Additionally, in the open ongoing studies, patients were assessed by biopsy and no evidence of dysplastic or neoplastic endocrine growth was found.

Prevention of Gastroduodenal Lesions and Dyspeptic Symptoms Associated with Non-Selective NSAIDs in Increased Risk Patients with a Need for Continuous Nonselective NSAID Treatment

Two randomised, double-blind, multicentre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions. The primary endpoint for both studies was the 'therapeutic failure' rate after 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.

<u>Study 205/2000</u>

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 Table 6.

Table 6: Results, Efficacy

	Time Interval (months)	Pantoprazole	Misoprostol	
Total numbers 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 end point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000

A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20 mg daily (n = 196), pantoprazole 40 mg daily (n = 199) or omeprazole 20 mg daily (n = 200). Efficacy results are shown in Table 7.

Table 7: Results, Efficacy

	Time Interval (months)	Pantoprazole 20 mg	Pantoprazole 40 mg	Omeprazole 20 mg
Total numbers 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 hours, with a C_{max} of approximately 1.2 microgram/mL following a 20 mg dose. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10–80 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 area under the curve (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.

Metabolism

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite in both the serum and urine is desmethyl-pantoprazole which is conjugated with the sulfate. The half-life of the main metabolites (approximately 1.5 hours) is not much longer than that of pantoprazole.

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

Excretion

Pantoprazole is rapidly eliminated from serum. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole; the rest are excreted with the faeces. Terminal half-life is approximately one hour and clearance is approximately 0.1 L/hour/kg. In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between seven and nine hours and the AUC values are increased by a factor of six to eight 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 threefold in patients with mild hepatic impairment and fivefold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 hours in mild hepatic impairment and six hours in severe hepatic impairment compared with 1.1 hours in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

pantoprazole 200 mg/kg/day 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 (50–1,200 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 7–100 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 showed 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.

General Toxicity

<u>Gastrointestinal System</u>

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 two-fold increase was observed in study RR126/97 after up to five 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 two-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 four weeks.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

See Section 4.5-Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blisters (Al/Al) of 5 or 30 tablets.

Not all strengths and/or pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

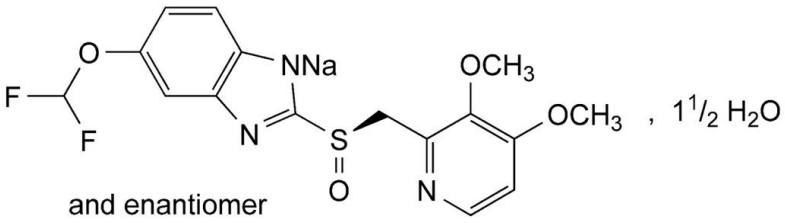
In Australia, any used medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical Name: Sodium 5-(difluoromethoxy)-2-[(*RS*)-[(3,4-dimethoxypyridin-2-yl) methyl]sulfinyl] benzimidazol-1-ide sesquihydrate

Structural Formula:



Molecular Formula: $C_{16}H_{14}F_2N_3NaO_4S \cdot 1½\ H_2O$

Molecular Weight: 432.4

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

15 October 2013

10 DATE OF REVISION

26 July 2018

Summary table of changes

Section Changed	Summary of new information
All	Product Information reformat and minor editorial changes
4.4	Addition of 'Effects on laboratory tests'
4.8	Additional adverse effects and addition of Apotex Medical Information for reporting of Adverse Drug Reaction Reporting
All	Change of trade name to PANTOPRAZOLE APOTEX
2 & 3	Change to tablet description
6.4	Change in storage temperature from 'Store below 30°C' to 'Store below 25°C'