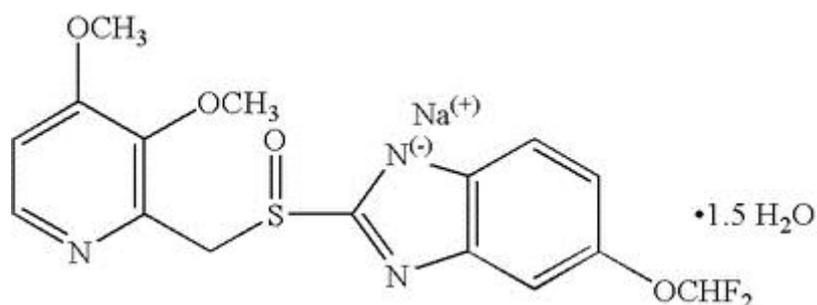**PRODUCT INFORMATION**
PANTOPRAZOLE SANDOZ 20mg/40mg ENTERIC COATED TABLETS

NAME OF THE MEDICINE

Pantoprazole (as sodium sesquihydrate)

5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole, sodium salt, sesquihydrate

CAS Number: 164579-32-2 (pantoprazole sodium sesquihydrate)

Empirical formula: $C_{16}H_{14}F_2N_3NaO_4S$. $1.5H_2O$ MW: 432

DESCRIPTION

Each Pantoprazole Sandoz 40mg enteric coated tablet contains 45.10mg of pantoprazole sodium sesquihydrate equivalent to 40mg of pantoprazole.

Each Pantoprazole Sandoz 20mg enteric coated tablet contains 22.55mg pantoprazole sodium sesquihydrate equivalent to 20mg of pantoprazole.

Pantoprazole is a substituted benzimidazole which inhibits 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.

In addition to pantoprazole sodium sesquihydrate, these tablets also contain sodium carbonate anhydrous, microcrystalline cellulose, crospovidone, hydroxypropylcellulose, colloidal anhydrous silica, calcium stearate, Opadry complete film coating system 03B22011 Yellow, Eudragit L30D-55, and triethyl citrate.

PHARMACOLOGY

Pharmacodynamics

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 sulphenamide which binds to the H^+/K^+-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

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

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

Helicobacter pylori (*H pylori*) is associated with duodenal and gastric ulcer disease in about 95 and 70% of patients, respectively. *H pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H pylori* and gastric carcinoma. An attempt to eradicate *H pylori* is recommended in most patients with duodenal and gastric ulcer where the latter is not caused by NSAID ingestion (see DOSAGE AND ADMINISTRATION). In an experimental study in mice, pantoprazole at a dose of 100mg/kg t.i.d. increased the inhibitory potency of amoxicillin, clarithromycin and tetracycline against *Helicobacter felis*.

Pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h, with a C_{max} of approximately 1.2 μg/mL. Terminal half-life is approximately 1 h. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics do not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80mg) after both oral and intravenous 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.

The serum protein binding of pantoprazole is approximately 98%. 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.

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

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.

Following oral administration of Pantoprazole Sandoz 40mg to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of pantoprazole of approximately 2459.7ng/mL was achieved within approximately 3.07 hours (T_{max}).

Following oral administration of Pantoprazole Sandoz 40mg to healthy subjects under fed conditions, a mean peak plasma concentration (C_{max}) of pantoprazole of approximately 2685.9ng/mL was achieved within approximately 6.48 hours (T_{max}).

CLINICAL TRIALS

Eradication of H pylori: The clinical trial program of pantoprazole for eradication of *H pylori* has investigated four therapy combinations. A summary of the clinical trials is provided in the following tables:

Table 1: Summary of clinical trial program for eradication of *H. pylori* using three triple therapies combinations

Study BY1023/	Design	Therapy Scheme (mg per day)	Days of medication	n (MITT)	Indication (n)	Eradication rate (MITT)
Regimen: Pantoprazole/Amoxicillin/Clarithromycin (PAC)						
VMG405	Open	PAC-P 80/2000/1000-40	7/7/7-7	60	DU (60)	81.7 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	7/7/7-7	150	DU (297)	90.0 %
		PCM-P 80/1000/1000-40	7/7/7-7	147		89.8 %
BGSA010	Single Blind Randomized	PAC 80/2000/1000	14/7/7	33	DU (67)	78.8 %
		PAC 80/2000/1000	14/14/14	34		91.2 %
BF005	Double Blind Randomized	PAC 80/2000/1000	7/7/7	96	NUD (192)	75.0 %
		PAC 40/2000/1000	7/7/7	96		56.3 %
Regimen: Pantoprazole/Clarithromycin/Metronidazole (PCM)						
VMG401	Open	PCM 80/500/800	7/7/7	30	DU (8), GU (3) HU (6), FD (13)	80.0 %
VMG402	Double Blind Randomized	PCM 80/1000/1000	7/7/7	121	DU (244)	73.6 %
		PCM 80/1000/1000	14/14/10	123		74.8 %
VMG404	Open	PCM-P 80/1000/1000-40	14/14/10-14	62	DU (62)	74.2 %
VMG411	Open Randomized	PAC-P 80/2000/1000-40	See *results for PAC regime above*			
		PCM-P 80/1000/1000-40				
FK3049	Open Randomized	PCM-P 80/1500/1500-40	7/7/7/-21	136	DU (277)	89.0 %

		PC-P 80/1500-40	14/14/-14	141		58.9 %
Regimen: Pantoprazole/Amoxicillin/Metronidazole (PAM)						
VMG406	Open	PAM-P 80/2000/1000-40	7/7/7-21	48	DU (24), GU (24)	81.3 %
VMG407	Open	PAM-P 80/2250/1200-40	10/10/10-18	65	DU (65)	78.5 %
VMG409	Open	PAM 80/2000/1000	7/7/7	30	GU (6), HU (13) FD (11)	70.0 %

Table 2: A clinical trial comparing quadruple and triple therapies with or without pantoprazole

Study	Design	Therapy Scheme (mg per day)	Days of medication	n (ITT)	Indication	Eradication rate
Regimen: Pantoprazole/Bismuth/Metronidazole/Tetracycline (PBMT)						
96-AGPP-001	Open Randomised	PBMT 80/432/1000/2000	7/7/7	134	NUD	82%
		PAC 80/2000/1000	7/7/7	134	NUD	78%
		BMT 432/1000/2000	14/14/14	137	NUD	69%

P: pantoprazole	**DU:** duodenal ulcer
PAC: pantoprazole/amoxicillin/clarithromycin	**GU:** gastric ulcer
PCM: pantoprazole/clarithromycin/metronidazole	**HU:** history of ulcer
PAM: pantoprazole/amoxicillin/metronidazole	**HDU:** history of duodenal ulcer
PBMT: pantoprazole/bismuth/metronidazole/tetracycline	**NUD:** non ulcer dyspepsia
BMT: bismuth/metronidazole/tetracycline	**FD:** functional dyspepsia
PC: pantoprazole/clarithromycin	**GAS:** gastritis
MITT: modified intention to treat	**ERO:** erosions

Treatment of symptomatic reflux (GORD): The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least 3 months prior to entry into the study. Efficacy of pantoprazole 20mg is shown in Table 3.

Table 3 Efficacy of pantoprazole 20mg in the treatment of symptomatic reflux (GORD)						
	1 week			**2 weeks**		
Data Set	**Pantoprazole20**	**Placebo**	**P**	**Pantoprazole20**	**Placebo**	**P**
Per Protocol N = 211 (week 1) N = 204 (week 2)	69%	30%	P < 0.001	80%	46%	P < 0.001

Intention to Treat N = 219	67%	32%	P < 0.001	74%	43%	P < 0.001

Acute treatment of mild reflux oesophagitis: In two randomised, double-blind, multi-centre studies (BGSA006 and FK3034) 410 patients with mild GORD (Savary-Miller stage 1) were treated with either pantoprazole 20mg once daily before breakfast or ranitidine 300mg once daily at bedtime. Superiority of pantoprazole 20mg in terms of healing rates as compared to ranitidine after 4 and 8 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 oesophagitis [2] in controlled trials of 12 months duration (Evaluable Patients)				
Trial	**Pantoprazole 20mg/d**	**Pantoprazole 40mg/d**	**Ranitidine 150mg/d**	**Difference [90% CI]**
FK3028	25% (n=221)	22% (n=212)	—	2.7% [-5, 10]
FK3033	28% (n=203)	19% (n=193)	—	9% [1, 17]
BGSA008	35% (n=75)	—	72% (n=40)	37% [23, 52]
1. Endoscopically confirmed 2. Patients were enrolled in the study with Savary-Miller stage 2-3 refluxoesophagitis. 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 20mg and 40mg/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 40-80mg/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 40mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 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 non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment: Two randomised, double-blind, multi centre studies (205/2000 and 129/2000) examined the efficacy and safety of pantoprazole in the prevention of NSAID-associated gastroduodenal ulcers, petechiae, erosions and dyspeptic symptoms in patients with arthritis on continuous treatment with NSAIDs and an increased risk to develop gastrointestinal lesions.

The primary endpoint for both studies was the therapeutic failure rate after 6 months, defined as endoscopic failure (i.e. more than 10 erosions or petechiae, peptic ulcer, reflux oesophagitis) or premature study termination due to at least likely related adverse event or due to severe gastrointestinal symptoms.

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

Results, Efficacy:				
	Time interval (months)	**Pantoprazole**	**Misoprostol**	
Total number of patients		257	258	
"In Remission" with regard to:		**[%]**	**[%]**	**p-value**
Therapeutic failure	0 — 6	89.3	70.3	< 0.001
Endoscopic failure	0 — 6	94.7	85.7	0.005

Symptomatic failure	0 — 6	98.5	91.7	0.002

Pantoprazole 20mg once daily was statistically significantly superior to misoprostol 200 µg twice daily with regard to therapeutic failure and to endoscopic failure. Reflux oesophagitis was included as an efficacy end-point in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

Study 129/2000: A total of 595 patients were included into the study. Patients were randomised to receive either pantoprazole 20mg daily (n=196), pantoprazole 40mg daily (n=199) or omeprazole 20mg daily (n=200). Efficacy results are shown in the table below.

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

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 associated with GORD
     ii. reflux oesophagitis
   - gastrointestinal lesions refractory to H_2 blockers
   - Zollinger-Ellison Syndrome.

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

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

3. For eradication of *Helicobacter pylori*, treatment with pantoprazole and one of the following combinations of antibiotics:
   - clarithromycin and amoxicillin or
   - clarithomycin and metronidazole or
   - amoxicillin and metronidazole

is recommended in cases of duodenal ulcer and gastric ulcer with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism.

4. Pantoprazole in combination with bismuth, metronidazole and tetracycline is indicated for the eradication of *Helicobacter pylori* associated with peptic ulcer disease with the objective of reducing the recurrence of peptic ulcers caused by this organism.

5. Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment.

CONTRAINDICATIONS

- Known hypersensitivity to pantoprazole, substituted benzimidazoles or any components of the formulation.
- 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 INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

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.

Gastrointestinal infections caused by bacteria
PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

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

Influence on vitamin B12 absorption
Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B_{12}) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption 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.

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

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.)

Interference with investigations for neuroendocrine tumours (See Effect on laboratory tests)
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of 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 health care professional should consider stopping pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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 1 year, patients should be kept under regular surveillance.

Patients being treated for symptomatic GORD with Pantoprazole Sandoz 20mg who do not respond after 4 weeks should be investigated.

Use in Pregnancy (Category B3)
Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450mg/kg/day, reduced foetal weight at $\geq$ 150mg/kg/day and delayed skeletal ossification and reduced pup growth at $\geq$ 15mg/kg/day. For the latter a no-effect dose was not established. Doses of 450mg/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.

Australian categorisation definition of:

Category B3:
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

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 30mg/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.

Paediatric Use

To date there is insufficient experience with treatment in children under 5 to justify a general recommendation.

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 200mg/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 1200mg/kg) (56E/96) and in mice at the high dose from the earlier micronucleus test (710mg/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.

Carcinogenity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200mg/kg/day gastric carcinoids were found after pantoprazole treatment at doses greater than 0.5mg/kg/day in females and greater than 5mg/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 5mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50mg/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 50mg/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 50mg/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 50mg/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 15mg/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.

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.

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 5mg/kg/day in rats and 2.5mg/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 160mg (about 4 and 15mg/kg) orally and 60mg (about 6mg/kg) IV). No ophthalmological changes or changes in electroretinographs were observed in cynomolgus monkeys at IV doses of up to 15mg/kg/day for 4 weeks.

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 ADVERSE EFFECTS). If affected, patients should not drive or operate machines.

Effect on laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, pantoprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

INTERACTIONS WITH OTHER MEDICINES

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).

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) have been reported during concomitant treatment in the post-marketing period.

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, monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect of pantoprazole.

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.

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.

HIV Protease Inhibitors
It has been shown that co-administration of atazanavir 300mg/ritonavir 100mg with omeprazole (40mg once daily) or atazanavir 400mg with lansoprazole (60mg 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 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.

ADVERSE EFFECTS

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

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥ 10%; common: ≥ 1% and <10%; uncommon: ≥ 0.1% and <1%; rare ≥ 0.01% and <0.1%; very rare: <0.01%). 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
Not known: Parasthaesia

Gastrointestinal system disorders:
Uncommon: diarrhoea, nausea / vomiting, abdominal distension and bloating, drymouth, 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   disorders:
Uncommon: liver enzymes increased (transaminases, gamma-GT)
Rare: bilirubin increased
Very rare: hepatic 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 nutrition disorders:
Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes
Not known: hyponatraemia, hypomagnesaemia, hypocalcaemia in association with hypomagnesaemia, hypokalaemia

Musculoskeletal and connective tissue disorders:
Rare: arthralgia, myalgia
Very rare: pain including skeletal pain
Not known: muscle spasm as a consequence of electrolyte disturbances, fracture of wrist, hip and spine

Renal and urinary disorders:
Very rare: interstitial nephritis (with possible progression to renal failure)

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 pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence
Very rare: anxiety

Blood and lymphatic system disorders:
Rare: anaemia, agranulocytosis
Very rare: leukopenia, thrombocytopenia, pancytopenia

Resistance mechanism disorders:
Rare: sepsis

Respiratory system disorders:
Very rare: dyspnoea

Reproductive system and breast disorders:
Rare: gynaecomastia

Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash / exanthema / eruption
Rare: angioedema, urticaria
Very rare: flushing, severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity
Not known: Subacute cutaneous lupus erythematosus

Eye disorders:
Uncommon: visual disturbances (blurred vision)
Very rare: conjunctivitis

Table 6: 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 7: 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%0
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%)

NOTE: ---- Events reported by < 1%

DOSAGE AND ADMINISTRATION

<u>Adults</u>

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

Helicobacter pylori positive patients: in *H pylori* positive patients with gastric and duodenal ulcers, eradication of this microorganism by combination therapy should be achieved.
One of the following combinations of pantoprazole with antibiotics is effective:

a) *Pantoprazole Sandoz 40mg twice daily*:
plus amoxicillin 1000mg (2 x 500mg) twice daily
plus clarithromycin 500mg twice daily

b) *Pantoprazole Sandoz 40mg twice daily:*
plus metronidazole 400mg in the morning and 600mg at night
plus clarithromycin 500mg twice daily

c) *Pantoprazole Sandoz 40mg twice daily:*
plus amoxicillin 1000mg (2 x 500mg) twice daily
plus metronidazole 400mg in the morning and 600mg at night

d) *Pantoprazole Sandoz 40mg twice daily:*
plus bismuth subcitrate 108mg four times a day
plus metronidazole 200mg three times a day and 400mg at night
plus tetracycline 500mg (2 x 250mg) four times a day

In combination therapy for eradication of *H pylori* infection, the second Pantoprazole Sandoz tablet should be taken before the evening meal. The duration for combination therapy is 7 days. If further treatment with Pantoprazole Sandoz is indicated to ensure ulcer healing, dosage recommendations as listed below for duodenal and gastric ulcers should be followed.

Helicobacter pylori negative patients: in *H pylori* negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

Duodenal Ulcer: Pantoprazole Sandoz 40mg (1 tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing generally occurs within 2 weeks. If a 2 week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Gastric Ulcer: Pantoprazole Sandoz 40mg (1 tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing will usually be achieved in a further 4 weeks.

Lesions Refractory to H$_2$-Receptor Antagonists: Pantoprazole Sandoz 40mg (1 tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4 week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

Zollinger-Ellison Syndrome: The number of Pantoprazole Sandoz 40mg 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 Pantoprazole Sandoz 20mg tablet per day. If symptom control has not been achieved after four weeks treatment with pantoprazole 20mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one Pantoprazole Sandoz 20mg or 40mg tablet per day. A 4 week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80mg pantoprazole per 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 Sandoz 20mg or 40mg tablet per day is recommended, dependent upon patient response.

Prevention of gastroduodenal lesions and dyspeptic symptoms associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in increased risk patients with a need for continuous non-selective NSAID treatment. The recommended oral dosage is one Pantoprazole Sandoz 20mg tablet per day.

Infants and children

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

Use in the Elderly

The usual daily dose of 20mg or 40mg can be given. During combination therapy for the eradication of *H pylori*, elderly patients should receive the recommended pantoprazole dose of 40mg twice daily for a 1-week treatment period.

Use in patients with renal impairment

The usual daily dose of 20mg or 40mg can be given. Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe renal dysfunction as no data are available on efficacy and safety in this population.

<u>Use in patients with hepatic impairment</u>

Combination therapy for eradication of *H pylori* should not be used in patients with moderate to severe hepatic dysfunction as no data are available on efficacy and safety in this population.

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see CONTRAINDICATIONS).

With milder forms of liver disease, the minimum effective dose has not been determined and the initial dose should be reduced.

<u>Monitoring Advice</u>

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

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

There are no known symptoms of overdosage in humans. In individual cases, 240mg 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.

PRESENTATION AND STORAGE CONDITIONS

Pantoprazole Sandoz 40mg - yellow and oval shaped enteric coated tablets containing 40mg pantoprazole (as sodium sesquihydrate).
Bottles (HDPE) or blister packs (Al/Al) of 5 or 30 tablets.

Pantoprazole Sandoz 20mg - yellow and oval shaped enteric coated tablets containing 20mg pantoprazole (as sodium sesquihydrate).
Bottles (HDPE)* or blister packs (Al/Al) of 30 tablets.

* Not currently marketed in Australia.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
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54 Waterloo Road,
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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG):
21/04/2009

Date of most recent amendment: 21/12/2016