PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Pantoprazole sodium (as pantoprazole sodium sesquihydrate)

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

Structural formula:

![Structural formula of pantoprazole sodium sesquihydrate]

Molecular formula: C_{16}H_{14}F_{2}N_{3}NaO_{4}S · 1.5H_{2}O  Molecular weight: 432.4

CAS Registry no.: 164579-32-2

DESCRIPTION

Salpraz 40mg enteric coated tablets contain 45.10mg of pantoprazole sodium sesquihydrate equivalent to 40mg of pantoprazole. Salpraz 20mg enteric coated tablets contain 22.55 mg 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, these tablets also contain the following inactive ingredients: cellulose-microcrystalline, lactose, croscarmellose sodium, silica-colloidal anhydrous, magnesium stearate (vegetable), Eudragit L30D-55, triethyl citrate and talc. The 20mg tablets contain OPADRY II complete film coating system 85F32081 Yellow as the coating agents, while 40mg tablets contain OPADRY II complete film coating system 85F32029 Yellow.

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

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 100 mg/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 Cmax of approximately 1.58 μg/mL. Terminal half-life is approximately 1.5 h.

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.

In studies in healthy volunteers, 2% of subjects showed a slower elimination of pantoprazole from serum/plasma, with an increase in terminal elimination half-life of up to 10 h. Patients with a half-life of greater than 3.5 h and with an apparent clearance of less than 2 L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver cirrhosis given a single 40 mg tablet, the half-life increases to between 7 and 9 h and
the AUC values are increased by a factor of 6-8 but the maximum serum concentration increases only slightly by a factor of 1.5 in comparison with healthy subjects. After a single 20 mg tablet, AUC increased 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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 $C_{\text{max}}$ in elderly volunteers compared with their younger counterparts is also not clinically relevant.

**CLINICAL TRIALS**

**Treatment of symptomatic reflux (GORD)**

The relief of symptoms of reflux in patients who showed no oesophageal lesions on endoscopy has been shown in the following double blind, multi-centre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled 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 20 mg is shown in Table 3.

| Table 3 Efficacy of Pantoprazole 20 mg in the treatment of symptomatic reflux |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | 1 week           |                 | 2 weeks          |                 |
| Data Set                        | Pantoprazole 20  | Placebo         | Pantoprazole 20  | Placebo         | P          | P          |
| Per Protocol                    |                  |                 |                  |                 |
| N = 211 (week 1)                | 69%              | 30%             | P < 0.001        | 80%             | 46%        | P < 0.001  |
| N = 204 (week 2)                |                  |                 |                  |                 |
| Intention to Treat              | 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 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 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)**

<table>
<thead>
<tr>
<th>Trial/Group</th>
<th>N</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>P&lt;0.05</th>
<th>P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGSA006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>101</td>
<td>73.3</td>
<td>83.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>100</td>
<td>49.0</td>
<td>69.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>P&lt;0.05</td>
<td>P&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FK3034</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>105</td>
<td>66.7</td>
<td>74.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>104</td>
<td>52.9</td>
<td>60.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>P&lt;0.05</td>
<td>P&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pantoprazole 20 mg/d</th>
<th>Pantoprazole 40 mg/d</th>
<th>Ranitidine 150 mg/d</th>
<th>Difference [90% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK3028</td>
<td>25% (n=221)</td>
<td>22% (n=212)</td>
<td>—</td>
<td>2.7% [-5, 10]</td>
</tr>
<tr>
<td>FK3033</td>
<td>28% (n=203)</td>
<td>19% (n=193)</td>
<td>—</td>
<td>9% [1, 17]</td>
</tr>
<tr>
<td>BGSA008</td>
<td>35% (n=75)</td>
<td>—</td>
<td>72% (n=40)</td>
<td>37% [23, 52]</td>
</tr>
</tbody>
</table>

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 mg and 40 mg/day doses were therapeutically equivalent based on the pre-defined equivalence criterion of the 90% confidence interval of the difference between doses being within ± 20%.

Four uncontrolled trials with varying periods of follow-up support the long-term efficacy of pantoprazole 40-80 mg/day in the maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis. Two of the trials included patients with gastric and duodenal ulcer. The incidence of relapse at 1 year was 12-15%, 2 years 22-25% and 6 years 40%.

Safety data is available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse effects (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see 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 20 mg daily (n=257) or misoprostol 200 μg twice daily (n=258). Efficacy of pantoprazole 20 mg is shown in the table below.

<table>
<thead>
<tr>
<th>Time interval (months)</th>
<th>Pantoprazole 20 mg</th>
<th>Misoprostol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>257</td>
<td>258</td>
</tr>
<tr>
<td>In Remission with regard to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic failure</td>
<td>0 — 6</td>
<td>89.3</td>
</tr>
<tr>
<td>Endoscopic failure</td>
<td>0 — 6</td>
<td>94.7</td>
</tr>
<tr>
<td>Symptomatic failure</td>
<td>0 — 6</td>
<td>98.5</td>
</tr>
</tbody>
</table>

Pantoprazole 20 mg 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 endpoint in the study which may have biased the results in favour of pantoprazole. A causal association between NSAIDs and reflux oesophagitis has not been established. In addition, proton pump inhibitors such as pantoprazole have documented beneficial treatment effects on reflux oesophagitis while misoprostol (a prostaglandin E1 analogue) has negligible therapeutic effects.

**Study 129/2000**

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

<table>
<thead>
<tr>
<th>Time interval (months)</th>
<th>Pantoprazole 20 mg</th>
<th>Pantoprazole 40 mg</th>
<th>Omeprazole 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>196</td>
<td>199</td>
<td>200</td>
</tr>
<tr>
<td>In Remission with regard to:</td>
<td>[%]</td>
<td>[%]</td>
<td>[%]</td>
</tr>
<tr>
<td>Therapeutic failure</td>
<td>0 — 6</td>
<td>89.8</td>
<td>93.1</td>
</tr>
<tr>
<td>Endoscopic failure</td>
<td>0 — 6</td>
<td>91.4</td>
<td>95.3</td>
</tr>
<tr>
<td>Symptomatic failure</td>
<td>0 — 6</td>
<td>98.1</td>
<td>100</td>
</tr>
</tbody>
</table>

All three treatments, 20 mg pantoprazole, 40 mg pantoprazole and 20 mg omeprazole, were proven to be of equivalent and high efficacy.

INDICATIONS

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
   - Duodenal ulcer
   - Gastric ulcer
   - Gastro-oesophageal reflux disease (GORD)
   - Symptomatic GORD. The treatment of heartburn and other symptoms associated with GORD
   - Reflux oesophagitis
   - Gastrointestinal lesions refractory to H₂ blockers
   - Zollinger-Ellison Syndrome

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

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

3. 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

Pantoprazole may not be used in cases of known hypersensitivity to any 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 atazanavir (see INTERACTIONS WITH OTHER MEDICINES).
PRECAUTIONS

Check the following before use

In the case of suspected gastric ulcer or reflux oesophagitis, gastric carcinoma and a malignant disease of the oesophagus should be excluded as treatment with pantoprazole could conceal the symptoms and may delay diagnosis.

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.

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

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

General Toxicity

Gastrointestinal system: Treatment with pantoprazole causes dose-dependent hypergastrinaemia as a result of inhibition of gastric acid secretion. Gastrin has a trophic effect on the gastric mucosa, and increases in gastric weight have been observed in rats and dogs to be dependent upon both dose and duration of treatment. Accompanying histopathological changes in the gastric mucosa were increased height, dilatation of fundic glands, chief cell hyperplasia and/or atrophy and parietal cell hyperplasia or vacuolation/degeneration. Increased density of enterochromaffin-like (ECL) cells was observed after 12 months treatment at dose levels from 5 mg/kg/day in rats and 2.5 mg/kg/day in dogs; all changes were reversible after various recovery periods. Since these gastric effects are a consequence of the pharmacological effect of acid secretion inhibition, no-effect doses were not established in all instances.

Although rats might be more susceptible to this effect than other species because of their high ECL cell density and sensitivity to gastrin, ECL cell hyperplasia occurs in other species, including mice and dogs, and has been observed in one of two clinical trials in which ECL cell density was measured (a 2-fold increase was observed in study RR126/97 after up to 5 years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplasic or neoplastic changes were observed in gastric endocrine
cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 2-week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40 and 160 mg (about 4 and 15 mg/kg) orally and 60 mg (about 6 mg/kg) IV). No ophthalmological changes or changes in electrophotographs were observed in cynomolgus monkeys at IV doses of up to 15 mg/kg/day for 4 weeks.

Effects on Fertility

Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats (estimated exposure at least 60-fold the clinical exposure from the 40 mg tablet) was found to have no effect on fertility and reproductive performance.

Use in Pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral rat studies, dose-dependent toxic effects were observed on foetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at 150 mg/kg/day or greater and delayed skeletal ossification and reduced pup growth at ≥ 15 mg/kg/day. For the latter a no-effect dose was not established. Doses of 450 mg/kg/day were maternotoxic and may have been associated with dystocia and incomplete parturition. Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentrations of pantoprazole in the fetus are increased shortly before birth regardless of the route of administration.

The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the 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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

Oral administration of pantoprazole to rats from late gestation to weaning at doses of 10 mg/kg/day or greater decreased pup growth. A transient effect on one of a series of development tests (startle response) was only evident in the 30 mg/kg/day group at an age when male and female offspring showed lower body weights, paralleled with lower brain weight, than the controls. The significance of these findings for humans is unknown, and there is currently no information on the safety of pantoprazole during breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the
Paediatric use

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

Carcinogenicity

A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day showed gastric carcinoids after pantoprazole treatment at doses greater than 0.5 mg/kg/day in females and greater than 5 mg/kg/day in males, with none observed in controls. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

In both male and female rats, the development of hepatocellular adenomas was increased at doses greater than 5 mg/kg/day and the development of hepatocellular carcinomas was increased at doses greater than 50 mg/kg/day. Hepatocellular tumours, which were also observed in female mice at oral doses greater than 25 mg/kg/day, may be associated with pantoprazole-induced increases in hepatic enzyme activity.

Treatment with pantoprazole at doses greater than 50 mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. Several studies in rats were conducted to investigate the effect of pantoprazole on the thyroid, the results of which suggested that the effect may be secondary to the induction of enzymes in the liver.

In a more recent carcinogenicity study, Fischer rats were studied using lower doses (5, 15 and 50 mg/kg). Gastric carcinoids were detected at all doses in females and at the 15 and 50 mg/kg doses in males and 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.

Genotoxicity

A number of in vitro and in vivo genotoxicity assays covering mutagenicity, clastogenicity and DNA damage end points were conducted on pantoprazole and the results were generally negative. Exposures achieved in the in vivo tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes in vitro, both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200 mg/kg/day pantoprazole for 14 days. However, no distinct DNA-adduct has been detected.

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

**INTERACTIONS WITH OTHER MEDICINES**

Pantoprazole is metabolized 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).

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. 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.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole), might be altered due to the decrease in gastric acidity.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore proton pump inhibitors, including pantoprazole, should not be co-administered with atazanavir (see CONTRAINDICATIONS).

**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:

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body As A Whole</td>
<td>fatigue, asthenia and increased sweating</td>
</tr>
<tr>
<td></td>
<td>reports of fever, anaphylactic reactions including anaphylactic shock and peripheral oedema</td>
</tr>
<tr>
<td>Rare</td>
<td>reports of substernal chest pain and hot flushes</td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
</tr>
</tbody>
</table>
### Cardiovascular disorder general
- Rare: hypertension
- Very rare: circulatory collapse

### Central and peripheral nervous system
- Uncommon: headache
- Very rare: dizziness
- Very rare: reduced movement and speech disorder

### Gastrointestinal system
- Uncommon: diarrhoea, severe eructation, constipation or flatulence, dry mouth, and upper abdominal pain
- Rare: nausea and vomiting
- Very rare: rectal disorder and colonic polyp
- Very rare: faecal discolouration and increased saliva

### Hearing and vestibular
- Very rare: tinnitus

### Immune system
- Very rare: anaphylactic reactions including anaphylactic shock

### Liver and biliary system
- Rare: increased liver enzymes (transaminases, gamma-GT) have occurred in patients receiving long-term maintenance therapy
- Very rare: hepatic failure, cholestatic hepatitis, bilirubinaemia and jaundice.

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

### Metabolic and nutritional disorder
- Very rare: hypertriglyceridaemia

### Musculoskeletal
- Rare: myalgia and arthralgia
- Very rare: pain including skeletal pain

### Renal and urinary
- Very rare: interstitial nephritis

### Platelet, bleeding, clotting disorders
- Very rare: thrombocytopenia and increased coagulation time

### Psychiatric disorders
- Rare: onset of depression, hallucination, disorientation and confusion, especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence
- Very rare: anxiety

### Red and white blood cell disorders
- Rare: anaemia
- Very rare: leukopenia

### Resistance mechanism disorders
- Rare: sepsis
### Respiratory system disorders

Very rare dyspnoea

### Skin and appendages

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>allergic reactions such as pruritus and skin rash</td>
</tr>
<tr>
<td>Rare</td>
<td>angioedema and urticaria</td>
</tr>
<tr>
<td>Very rare</td>
<td>severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity</td>
</tr>
</tbody>
</table>

### Special senses, other disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>metallic taste</td>
</tr>
</tbody>
</table>

### Vascular (extracardiac) disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>flushing</td>
</tr>
</tbody>
</table>

### Vision disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>disturbances in vision (blurred vision)</td>
</tr>
<tr>
<td>Very rare</td>
<td>conjunctivitis</td>
</tr>
</tbody>
</table>

---

### DOSAGE AND ADMINISTRATION

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

In H. pylori negative patients, the following dosage guidelines apply for monotherapy with pantoprazole.

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

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

**Lesions Refractory to H2-Receptor Antagonists.** Salpraz 40 mg (1 tablet) should be given once a day. In most patients freedom from symptoms is achieved rapidly and healing usually takes 4 weeks. If a 4-week period of treatment is not sufficient, healing is achieved in the majority of patients in a further 4 weeks. In a small group of patients, there may be benefit in extending pantoprazole therapy to a total of 12 weeks.

**Zollinger-Ellison Syndrome.** The number of Salpraz 40 mg tablets should be individually adjusted so that the acid output remains below 10 mmol/L. No fixed period of time is proposed for treatment of Zollinger-Ellison syndrome.

**GORD:**

**Symptomatic GORD (Treatment of symptomatic reflux).** The recommended dosage is one Salpraz 20 mg tablet per day. If symptom control has not been achieved after four weeks treatment with Salpraz 20 mg tablets daily, further investigation is recommended, for example endoscopy.
Treatment of reflux oesophagitis. The recommended oral dosage is one Salpraz 20 mg or 40 mg tablet per day. A 4-week period is usually required for healing, however if this is not sufficient, healing will usually be achieved within a further 4 weeks. This dosage may be increased up to 80 mg pantoprazole per day.

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

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

Use in Children

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

Use in the Elderly

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

Impaired Renal Function

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

Impaired Hepatic Function

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.

OVERDOSAGE

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

Contact the Poisons Information Centre on 131126 (Australia) for recommendation on the management and treatment of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Salpraz pantoprazole 40 mg enteric coated tablets contain 45.10 mg of pantoprazole sodium sesquihydrate and are available in both blister packs and bottles* of 5s* and 30s. The tablets are yellow to ochre and elongated.

Salpraz pantoprazole 20 mg enteric coated tablets contain 22.55 mg of pantoprazole sodium sesquihydrate and are available in both blister packs and bottles* of 5s* and 30s. The tablets are yellow to ochre and
elongated.

* Currently not marketed in Australia.

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited
Level 1, 30 The Bond
30 – 34 Hickson Road
Millers Point NSW 2000
ABN 93 002 359 739
www.alphapharm.com.au

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription only medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

SALPRAZ 20 mg tablet blister pack: 23/09/2009
SALPRAZ 20 mg tablet bottle: 30/06/2009
SALPRAZ 40 mg tablet blister pack: 23/09/2009
SALPRAZ 40 mg tablet bottle: 30/06/2009

DATE OF MOST RECENT AMENDMENT

04/10/2012