OZPAN Tablets

Pantoprazole sodium sesquihydrate

CAS Number: 138 786-67-1 (pantoprazole sodium)

DESCRIPTION

Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. The structure of pantoprazole sodium sesquihydrate is:

\[
\text{STRUCTURAL FORMULA OF PANTOPRAZOLE SODIUM SESQUIHYDRATE}
\]

The molecular weight of pantoprazole, sodium salt x 1.5 H₂O is 432.4.

Each tablet of OZPAN contains Pantoprazole sodium sesquihydrate equivalent to 20mg or 40mg of Pantoprazole

OZPAN contains the following inactive ingredients: Sodium carbonate anhydrous, Mannitol, Crospovidone, Hydroxypropyl cellulose, Cellulose - microcrystalline, Calcium stearate, Opadry 02H52369 Yellow, Methacrylic acid – ethyl acrylate copolymer (1:1), Triethyl citrate, sodium lauryl sulfate, Titanium dioxide, Iron oxide yellow, Talc - purified, Opacode S-1-17823 Black

PHARMACOLOGY

- Pharmacodynamic properties

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately \(\text{H}^+/\text{K}^+\)- 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 \(\text{H}^+/\text{K}^+\)- 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.

- **Pharmacokinetic properties**

  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 1.2 pg/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 80 mg) 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 (δ 23%) with once daily dosing.

  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 Cmax 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 1:** Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux

<table>
<thead>
<tr>
<th>Data Set</th>
<th>1 week</th>
<th></th>
<th>2 weeks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pantoprazole 20 mg</td>
<td>Placebo</td>
<td>P</td>
<td>Pantoprazole 20 mg</td>
</tr>
<tr>
<td>Per Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 211 (week 1)</td>
<td>69%</td>
<td>30%</td>
<td>P &lt; 0.001</td>
<td>80%</td>
</tr>
<tr>
<td>N = 204 (week 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to Treat</td>
<td>67%</td>
<td>32%</td>
<td>P &lt; 0.001</td>
<td>74%</td>
</tr>
</tbody>
</table>

**Acute treatment of mild reflux oesophagitis**

In two randomised, double-blind, multi-centre studies, 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 2: Endoscopic healing of stage 1 oesophagitis (Intention-to-Treat)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% Patients Healed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>101</td>
<td>73.3</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>100</td>
<td>49.0</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>105</td>
<td>66.7</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>104</td>
<td>52.9</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>P &lt; 0.05</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 3: Incidence of relapse\(^a\) (%) of reflux oesophagitis\(^b\) in controlled trials of 12 months duration (Evaluable Patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pantoprazole 20 mg/day</th>
<th>Pantoprazole 40 mg/day</th>
<th>Ranitidine 150 mg/day</th>
<th>Difference [90% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25% (n=221)</td>
<td>22% (n=212)</td>
<td>-</td>
<td>2.7% [-5.10]</td>
</tr>
<tr>
<td>2</td>
<td>28% (n=203)</td>
<td>19% (n=193)</td>
<td>-</td>
<td>9% [1.17]</td>
</tr>
<tr>
<td>3</td>
<td>35% (n=75)</td>
<td>-</td>
<td>72% (n=40)</td>
<td>37% [23.52]</td>
</tr>
</tbody>
</table>

\(a\) Endoscopically confirmed

\(b\) 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 are available from the 1584 patients involved in the 7 long-term clinical studies. 904 patients have been treated with pantoprazole for at least 1 year, and 273, 112, 68, 47 and 17 have been treated for at least 2, 3, 4, 5 and 6 years, respectively. In total, 108 (6.8%) patients experienced serious adverse events (EC definition), of which all but 6 were classified as being causally unrelated to pantoprazole (4 cases with 40 mg pantoprazole: colonic polyp; abdominal pain and rectal disorder; diarrhoea and abdominal pain, sepsis versus 2 cases with high-dose pantoprazole: anaemia and hypertension (see Adverse Reactions). 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 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 1

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.

Results, Efficacy:

<table>
<thead>
<tr>
<th>Time interval (months)</th>
<th>Pantoprazole</th>
<th>Misoprostol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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>89.3</td>
<td>70.3</td>
</tr>
<tr>
<td>Endoscopic failure</td>
<td>0 – 6</td>
<td>94.7</td>
<td>85.7</td>
</tr>
<tr>
<td>Symptomatic failure</td>
<td>0 – 6</td>
<td>98.5</td>
<td>91.7</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 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 2**

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**

**OZPAN** is indicated for:

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 nonsteroidal 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 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.

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin (vitamin B₁₂) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B₁₂ 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 B₁₂) deficiency following acid-blocking therapy have been reported.

Use of Pantoprazole enteric coated tablets 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.

- Carcinogenicity, Mutagenicity and Impairment of Fertility

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.

Mutagenesis: Pantoprazole was found to be negative in the following studies: *in vivo* chromosome aberration assay in rat and bone marrow, mouse lymphoma test and a gene mutation test in Chinese hamster ovary cells (*in vitro*). In addition, toxicokinetic studies were conducted in rats at the doses used in the bone marrow assay (50 to 1200 mg/kg) and in mice at the high dose from the earlier micronucleus test (710 mg/kg). Pantoprazole exposure was high with the respective rat and mouse plasma AUCs being 7 to 100 and 9- to 12-fold the clinical exposure from a 40 mg tablet.

Carcinogenicity: A two year oral carcinogenicity study in Sprague Dawley rats at doses up to 200 mg/kg/day 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.

Impairment of 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 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 one study after up to 5 years of treatment with regular and high doses, but no increase was observed in a second study). No dysplasic or neoplastic changes were observed in gastric endocrine cells in either study.

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

**USE DURING PREGNANCY (Category B1)**

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 fetuses and pups: increased pre- and postnatal deaths at 450 mg/kg/day, reduced fetal weight at > 150 mg/kg/day 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 fetus.
USE DURING LACTATION

A pen/post-natal study in rats found that treatment with pantoprazole 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 risks.

USE IN CHILDREN

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

INTERACTIONS WITH OTHER DRUGS

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.

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.

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 REACTIONS

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 postmarketing surveillance:

**Body as a whole**

Fatigue, asthenia and increased sweating

Rare reports of fever, anaphylactic reactions including anaphylactic shock and peripheral oedema

Very rare reports of substernal chest pain, increased body temperature and hot flushes

**Cardiovascular disorders general**

Rare reports of hypertension

Very rare reports of circulatory collapse

**Central and peripheral nervous system disorders**

Headache

Uncommon reports of dizziness

Very rare reports of reduced movement and speech disorder

**Gastrointestinal system disorders**

Diarrhoea, severe eructation, constipation or flatulence, dry mouth, and upper abdominal pain.

Uncommon reports of nausea and vomiting

Rare reports of rectal disorder and colonic polyp

Very rare reports of faecal discoloration and increased saliva

**Hearing and vestibular disorders**

Very rare reports of tinnitus

**Immune system disorders**

Very rare reports of anaphylactic reactions including anaphylactic shock.

**Liver and biliary system disorders**

Rare reports of increased liver enzymes (transaminases, gamma-GT) have occurred in patients receiving long-term maintenance therapy.

Very rare reports of 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 disorders**
Rare reports of hypertriglyceridaemia

**Musculoskeletal**
Rare reports of myalgia and arthralgia
Very rare reports of pain including skeletal pain

**Renal and urinary disorders**
Very rare reports of interstitial nephritis

**Platelet, bleeding, clotting disorders**
Very rare reports of thrombocytopenia and increased coagulation time

**Psychiatric disorders**
Rare reports of 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 reports of anxiety

**Red and white blood cell disorders**
Rare reports of anaemia
Very rare reports of leukopenia

**Resistance mechanism disorders**
Rare reports of sepsis

**Respiratory system disorders**
Very rare reports of dyspnoea

**Skin and appendages**
Uncommon reports of allergic reactions such as pruritus and skin rash
Rare reports of angioedema and urticaria
Very rare reports of severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell Syndrome and photosensitivity

**Special senses, other disorders**
Metallic taste
Very rare reports of changes to the senses of smell and taste

**Vascular (extracardiac) disorders**
Very rare reports of flushing

**Vision disorders**
Uncommon reports of disturbances in vision (blunted vision)
Very rare reports of conjunctivitis

Table 4: 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

<table>
<thead>
<tr>
<th>Event</th>
<th>PCM/T* n=725</th>
<th>PAC n=492</th>
<th>PAM n=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>4.8</td>
<td>10.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Taste bitter</td>
<td>4.0</td>
<td>3.0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.7</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Taste metallic</td>
<td>2.1</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>1.9</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1.8</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.4</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Tongue pain</td>
<td>1.2</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Liver enzymes increased</td>
<td>1.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1.1</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Loose stools</td>
<td>1.0</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Oral moniliasis</td>
<td>1.0</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Buccal inflammation</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Exanthemata</td>
<td>0.4</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Heartburn</td>
<td>0.4</td>
<td>0.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0.1</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Rash</td>
<td>0.1</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>At least one of the above</td>
<td>34</td>
<td>29</td>
<td>20</td>
</tr>
</tbody>
</table>

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

Table 5: Adverse events (≥ 1%) reported in a clinical trial comparing quadruple and triple therapies for *H pylori* eradication regardless of causality

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>PBMT (n=422)</th>
<th>BMT (n=600)</th>
<th>PAC (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin &amp; appendages disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>7 (1.7%)</td>
<td>16 (2.7%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Pruritus ani</td>
<td>---</td>
<td>7 (1.2%)</td>
<td>---</td>
</tr>
<tr>
<td>Central &amp; peripheral nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>49 (11.6%)</td>
<td>65 (10.8%)</td>
<td>38 (10.3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (7.1%)</td>
<td>38 (6.3%)</td>
<td>25 (6.8%)</td>
</tr>
<tr>
<td>Special senses other, disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste pervasion</td>
<td>45 (10.7%)</td>
<td>65 (10.8%)</td>
<td>67 (18.2%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>11 (2.6%)</td>
<td>19 (3.2%)</td>
<td>17 (4.6%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>---</td>
<td>8 (1.3%)</td>
<td>---</td>
</tr>
<tr>
<td>Depression</td>
<td>---</td>
<td>---</td>
<td>4 (1.1%)</td>
</tr>
</tbody>
</table>
### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Row 1 (%)</th>
<th>Row 2 (%)</th>
<th>Row 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>49 (11.6%)</td>
<td>56 (9.3%)</td>
<td>37 (10.1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (9.0%)</td>
<td>58 (9.7%)</td>
<td>34 (9.2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27 (6.4%)</td>
<td>37 (6.2%)</td>
<td>24 (6.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (1.7%)</td>
<td>12 (2.0%)</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Faeces discoloured</td>
<td>7 (1.7%)</td>
<td>18 (3.0%)</td>
<td>---</td>
</tr>
<tr>
<td>Tongue discolouration</td>
<td>10 (2.4%)</td>
<td>11 (1.8%)</td>
<td>---</td>
</tr>
<tr>
<td>Mouth dry</td>
<td>---</td>
<td>13 (2.2%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>---</td>
<td>---</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>---</td>
<td>6 (1.0%)</td>
<td>---</td>
</tr>
</tbody>
</table>

### Respiratory system disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Row 1 (%)</th>
<th>Row 2 (%)</th>
<th>Row 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngitis</td>
<td>8 (1.9%)</td>
<td>9 (1.5%)</td>
<td>7 (1.9%)</td>
</tr>
</tbody>
</table>

### Body as a whole - general disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Row 1 (%)</th>
<th>Row 2 (%)</th>
<th>Row 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-like symptoms</td>
<td>15 (3.6%)</td>
<td>12 (2.0%)</td>
<td>14 (3.8%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (1.2%)</td>
<td>---</td>
<td>4 (1.1%)</td>
</tr>
</tbody>
</table>

### Resistance mechanism disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Row 1 (%)</th>
<th>Row 2 (%)</th>
<th>Row 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moniliasis</td>
<td>6 (1.4%)</td>
<td>---</td>
<td>5 (1.4%)</td>
</tr>
</tbody>
</table>

--- Events reported by < 1%

### DOSAGE AND ADMINISTRATION

OZPAN 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. OZPAN** 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. OZPAN** 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 H$_2$-Receptor Antagonists. OZPAN** 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 OZPAN 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 OZPAN 20 mg tablet per day. If symptom control has not been achieved after four weeks treatment with OZPAN 20 mg tablets daily, further investigation is recommended, for example endoscopy.

Treatment of reflux oesophagitis: The recommended oral dosage is one OZPAN 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 OZPAN 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 OZPAN 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. 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.

Further information for advice on management can also be obtained from the Poisons Information Centre on 131 126 for advice about treatment and management of the overdose.

PRESENTATION AND STORAGE CONDITIONS

OZPAN 20 mg tablets are available as yellow-coloured, enteric-coated oval-shaped, biconvex tablets imprinted with ‘II’ in black ink on one side and plain on other side.

OZPAN 40 mg tablets are available as yellow coloured, enteric-coated oval shaped, biconvex tablets imprinted with ‘IV’ in black ink on one side and plain on other side.

The tablets are supplied in cold form blister pack containing 30 tablets of 20 mg and 40 mg tablets.

Store below 25 °C.

NAME AND ADDRESS OF THE SPONSOR

Ranbaxy Australia Pty Ltd.
Suite 4.02, Building D, Level 4
12 – 24 Talavera Road
North Ryde, NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

S4

Date of approval

27 May 2009

Date of most recent amendment

16 Jul 2010