

Data Sheet

Pantocid I.V.[®]

Pantoprazole powder for Injection

Presentation

Pantocid I.V. is available as single vials of Pantoprazole for Injection 40 mg. Each vial of Pantocid I.V. contains 45.12 mg pantoprazole sodium sesquihydrate (equivalent to pantoprazole 40mg) as lyophilized powder.

The molecular weight of pantoprazole sodium is 405.5. Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. Pantoprazole sodium is a white to off-white amorphous hygroscopic powder. Solubility is low at neutral pH and increases with increasing pH.

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). Oral and intravenous pantoprazole 40 mg/day for 5 days had equivalent effect on intra-gastric pH in 20 healthy adult male volunteers in a randomised, open, 2-period crossover trial with 14-day wash-out. The pre-defined equivalence range was $\pm 20\%$ for % time with pH < 3 and ± 1 pH unit for 24 h median pH. The 24 h median pH on day 5 was 2.7 on oral treatment and 3.2 on intravenous treatment.

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.

Pharmacokinetics

A considerably higher C_{max} occurs after intravenous administration compared with oral administration. In a study in healthy volunteers given 40 mg/day for 5 days, the steady state C_{max} was 5.9 mg/L after intravenous administration and 1.7 mg/L after oral administration. 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.

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 impairment, pantoprazole elimination is significantly delayed. After a 40 mg tablet, AUC increased by a factor of 6-8 and terminal half life increased from 1 h to 7-9 h in patients with liver cirrhosis 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.

Clinical Trials

Two uncontrolled trials in adults assessed the efficacy of pantoprazole 40 mg/day, administered intravenously for 5-7 days then orally for 3-7 weeks, in the endoscopic healing of Savary-Miller stage 2-3 reflux oesophagitis (Table). Using historical data, it was concluded that the IV plus oral regimen was at least equivalent to an exclusively oral regimen. The criterion for at least equivalence was: lower limit of 90% confidence interval of the difference, (IV + oral) - oral, > -15%.

Table - Pantoprazole 40 mg/day (IV plus oral) In Endoscopic Healing Of Stage 2-3 Oesophagitis (Intention To Treat¹)

Trial	N	% Patients Healed	
		4 weeks	8 weeks
FK3050	176	65	75
BAT010	110	77	85
Historical (oral) ²	357	64	77

¹ Protocol violators counted as non-responders

² Trials FK3005, FK3009

Indications

Short-term use where oral therapy is not appropriate for:

1. Symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
 - Duodenal ulcer
 - Gastric ulcer
 - Reflux oesophagitis
 - Gastrointestinal lesions refractory to H2 blockers
 - Zollinger-Ellison Syndrome
2. Maintenance of healed reflux oesophagitis in patients previously treated for moderate to severe reflux oesophagitis.

Note: Patients whose gastric or duodenal ulceration is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to anti-secretory drugs, whether on first presentation or recurrence.

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**).

Precautions

Check the following before use:

The intravenous administration of PANTOCID powder for injection is recommended only if oral application is not appropriate.

In the presence of any alarm symptom (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.

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 (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.

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.

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 dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular toxicity and dermal phototoxicity/sensitivity: Studies have shown that pantoprazole is retained in low levels in the eyes and skin of pigmented rats. It is likely that the retention reflects a reversible association with melanin. Animal studies investigating the potential for phototoxicity/photosensitivity have not been conducted. A 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 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 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 in Lactation

A peri/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 breastfeeding 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

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, nifedipine, phenytoin, theophylline, and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyl oestradiol). 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 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

PANTOCID powder for injection is well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity. The following adverse reactions have been reported in patients receiving pantoprazole alone or in 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 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 discolouration and increased saliva

Hearing and vestibular disorders

- Very rare reports of tinnitus

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 oral administration 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

- Rare reports of thrombophlebitis associated with the use of injection only
- Very rare reports of flushing

Vision disorders

- Uncommon reports of disturbances in vision (blurred vision)
- Very rare reports of conjunctivitis

Dosage and Administration

Duodenal ulcer, gastric ulcer, gastrointestinal lesions refractory to H ₂ blockers, Zollinger-Ellison syndrome	40 mg per day
Reflux oesophagitis	20-40 mg per day

Intravenous PANTOCID should be replaced with oral therapy as soon as practicable.

Preparation for Use

A ready-to-use solution is prepared by injecting 10 mL Sodium Chloride Intravenous Infusion 0.9% into the vial containing the dry powder. This solution may be administered directly or may be administered after mixing with 100 mL Sodium Chloride Intravenous Infusion 0.9% or 100 mL Glucose Intravenous Infusion 5 or 10%. The resulting solution should be used within 3 hours, -stored at 2-8°C and is for SINGLE USE ONLY.

After preparation, the solution should be administered over 2 to 15 minutes.

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 initial dose should be reduced.

Instructions for use and handling

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C - 8°C for not more than 3 hours.

This product contains no antimicrobial agent. Pantocid injection is for single use in one patient only. Any unused product remaining or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed), should be discarded.

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.

Contact the Poisons Information Centre for advice on the management of an overdose.

Pharmaceutical Precautions

Pantocid I.V. should be stored at below 25°C. Reconstituted solution (see 'Preparation of Use' above) should be stored at 2-8°C and used within 3 hours.

Medicine Classification

Prescription Medicine

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