APO-PANTOPRAZOLE HEARTBURN RELIEF

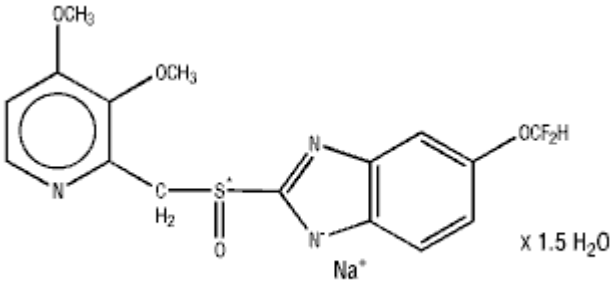
NAME OF THE MEDICINE

Pantoprazole sodium sesquihydrate.

Chemical Name: 1) 1H-Benzimidazole, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-, sodium salt, hydrate (2:3)

2) 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl] sulfinyl]benzimidazole, sodium salt, sesquihydrate

Structural Formula:



Pantoprazole sodium sesquihydrate

Molecular Formula: C16H14F2N3NaO4S.1.5 H2O

Molecular Weight: 432.4

CAS Registry Number: 164579-32-2

DESCRIPTION

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.

Each enteric coated tablet contains the active ingredient pantoprazole (as sodium sesquihydrate). In addition, each enteric coated tablet contains the following inactive ingredients: lactose anhydrous, crospovidone, microcrystalline cellulose, magnesium stearate, hypromellose, macrogol 8000, anhydrous sodium carbonate, methacrylic acid copolymer, triethyl citrate, talc-purified, titanium dioxide and iron oxide 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 sulfenamide which binds to the H^+/K^+-ATPase, thus inhibiting the proton pump and causing potent and long lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin). Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic, effect can only be achieved in the acid

secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

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

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 hours, with a Cmax of approximately 1.2 microgram/mL. Terminal half-life is approximately one hour. Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/hour/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 (IV) administration. Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on area under the curve (AUC), maximum serum concentrations and thus bioavailability.

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 sulfate. The half-life of the main metabolites (approximately 1.5 hours) 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. After a single 20 mg tablet, AUC increased threefold in patients with mild hepatic impairment and fivefold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 hours in mild hepatic impairment and six hours in severe hepatic impairment compared with 1.1 hours in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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

The slight increase in AUC and 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, multicentre, placebo controlled study (245/98) using pantoprazole 20 mg once daily. Overall, 219 patients were enrolled into the study. Each patient was to have a normal oesophagus as assessed by endoscopy and to have suffered from at least one episode of heartburn of at least moderate intensity on all three days prior to inclusion into the study. Additionally, patients were to have a history of reflux symptoms (heartburn, acid eructation, pain on swallowing) for at least three months prior to entry into the study. Efficacy of pantoprazole 20 mg is shown in Table 1.

Pantoprazole **Table 1**
Efficacy of Pantoprazole in Treatment of Symptomatic GORD

Data set	1 week			2 weeks		
	Pantoprazole 20	Placebo	p	Pantoprazole 20	Placebo	p
Per protocol n = 211 (week 1) n = 204 (week 2)	69%	30%	p < 0.001	80%	46%	p < 0.001
Intention to treat n = 219	67%	32%	p < 0.001	74%	43%	p < 0.001

INDICATIONS

The symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastroesophageal reflux disease (GORD).

CONTRAINDICATIONS

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 coadministered with atazanavir (see Interactions).

PRECAUTIONS

Patients should be referred to their doctor for review if they:

- have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, malaena, gastric ulcer is suspected or present or gastrointestinal surgery, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. In these cases, malignancy should be excluded;
- have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms;
- are being treated for symptomatic GORD and require pantoprazole for more than 14 days;
- have jaundice or other severe hepatic impairment (e.g. cirrhosis); or
- have any other significant medical condition.

Patients should consult their doctor before taking this product if they are due to have an endoscopy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity assays covering mutagenicity, clastogenicity and DNA damage endpoints were conducted on pantoprazole and the results were generally negative. Exposures achieved in the *in vivo* tests in mice and rats were well in excess of exposures expected clinically. However, pantoprazole was clearly positive in carefully conducted cytogenetic assays in human lymphocytes *in vitro,* both in the presence and absence of metabolic activation. Omeprazole was also positive in a comparable test conducted in the same laboratory, suggesting a possible class effect. A minute amount of radioactivity was bound to rat hepatic DNA after treatment with pantoprazole 200 mg/kg/day for 14 days. 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 1,200 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 in 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 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 the 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 two-fold increase was observed in study RR126/97 after up to five years of treatment with regular and high doses, but no increase was observed in study RR125/97). No dysplastic or neoplastic changes were observed in gastric endocrine cells in either study.

Ocular Toxicity and Dermal Phototoxicity/Sensitivity

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

A two week dog study, conducted specifically to investigate the effects on the eye and ear, did not reveal any changes relating to pantoprazole treatment, but the doses chosen were relatively low (40

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

Use in Pregnancy (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In oral studies in rats, dose dependent toxic effects were observed on fetuses and pups: increased prenatal and postnatal deaths (450 mg/kg/day), reduced fetal weight (greater than or equal to 150 mg/kg/day) and delayed skeletal ossification and reduced pup growth (greater than or equal to 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 foetus are increased shortly before birth regardless of the route of administration. The significance of these findings in humans is unclear. As there is no information on the safety of the drug during pregnancy in women, pantoprazole should not be used during pregnancy unless the benefit clearly outweighs the potential risk to the foetus.

Use in Lactation

A perinatal/postnatal 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 bodyweights, 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.

Paediatric Use

To date there has been limited experience with treatment in children and adolescents under 18 years of age..

INTERACTIONS WITH OTHER MEDICINES

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and the low dose oral contraceptive Triphasil (levonorgestrel and ethinyloestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

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 postmarketing 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.

Concomitant use of proton pump inhibitors with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

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, itraconazole, posaconazole, erlotinib) might be altered due to the decrease in gastric acidity.

Four crossover pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxycillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

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

ADVERSE EFFECTS

Pantoprazole tablets are well tolerated. Most of the adverse reactions seen with treatment were of mild or moderate intensity in clinical trials and postmarketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole.

Adverse reactions within each body system are listen in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare: ≥0.01% and <0.1%; very rare: < 0.01%). These include the following:

General disorders and administration site conditions

Uncommon: fatigue, malaise, asthenia and increased sweating
Rare: fever and peripheral oedema
Very rare: reports of substernal chest pain and hot flushes

Cardiovascular disorders general

Rare: hypertension
Very rare: circulatory collapse

Nervous system disorders

Uncommon: headache, dizziness.
Rare: taste disorders
Very rare: reduced movement and speech disorder, changes the sense of smell and taste
Not known: metallic taste

Gastrointestinal system disorders

Uncommon: diarrhoea, nausea, vomiting, abdominal pain and discomfort, constipation, dry mouth

Rare: rectal disorder and colonic polyp
Very rare: faecal discolouration and increased saliva
Not known: flatulence, severe eructation

Hearing and vestibular disorders

Very rare: tinnitus.

Immune system disorders

Rare: hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Hepatobiliary disorders

Uncommon: liver enzymes increased (transaminases, gamma-GT)
Rare: bilirubinaemia increased
Very rare: hepatocellular failure, cholestatic hepatitis, and jaundice
Not known: hepatocellular injury

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

Metabolism and nutrition disorders

Rare: hyperlipidaemias and lipid increases (triglycerides, cholesterol), weight changes
Not Known: hyponatraemia, hypomagnesaemia

Musculoskeletal and connective tissue disorders

Rare: myalgia and arthralgia
Very rare: pain including skeletal pain

Renal and urinary disorders

Very rare: interstitial nephritis

Blood and lymphatic system disorders

Rare: anaemia agranulocytosis
Very rare: leukopenia, thrombocytopenia, pancytopenia, increased coagulation time

Psychiatric disorders

Uncommon: sleep diorders
Rare: depression, hallucination, disorientation and confusion, especially in predisposed patients, as well as aggravation of these symptoms in the case of pre-existence.
Very rare: anxiety.

Resistance mechanism disorders

Rare: sepsis.

Respiratory system disorders

Very rare: dyspnoea.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash, exanthema/eruption
Rare: angioedema and urticaria,
Very rare: severe skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, Lyell syndrome and photosensitivity.

Reproductive system and breast disorders

Rare: gynaecomastia

Eye disorders

Uncommon: disturbances in vision (blurred vision).
Very rare: conjunctivitis.

DOSAGE AND ADMINISTRATION

APO-Pantoprazole Heartburn Relief is indicated for use in adults 18 years of age and over. Pantoprazole tablets should not be chewed or crushed, but swallowed whole with a little water.

Gastroesophageal Reflux Disease

Symptomatic Gastroesophageal Reflux Disease (Treatment of Symptomatic Reflux)

The recommended dosage is one pantoprazole 20 mg tablet per day for at least 7 days, and up to 14 days. If symptom control has not been achieved after two weeks of continuous treatment with pantoprazole 20mg tablets daily, patients should be referred to their doctor.

Use in Children

There are limited data currently available on the use of pantoprazole in children. Pantoprazole is not recommended for use in children and adolescents under 18 years of age.

Use in the Elderly

No dose adjustment is necessary in elderly patients.

Impaired Renal Function

No dose adjustment is required when pantoprazole is administered to patients with impaired renal function.

Impaired Hepatic Function

Pantoprazole is contraindicated in patients with cirrhosis or severe liver disease (see **CONTRAINDICATIONS**).
No dose adjustment is required when pantoprazole is administered to patients with milder forms of impaired liver function.

OVERDOSAGE

Symptoms

There are no known symptoms of overdosage in humans. In individual cases 240 mg has been administered IV or orally and was well tolerated.

Treatment

Standard detoxification procedures apply.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

The enteric coated tablets are intended for oral administration.

APO-Pantoprazole Heartburn Relief Tablets 20 mg
Yellow, oval, biconvex, enteric-coated tablets engraved “APO” on one side, “20” on the other side.

Blisters (Alu/Alu) of 7 or 14 tablets: AUST R 156332.

Store below 25°C. Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
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Australia

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POISON SCHEDULE OF THE MEDICINE

S3: Pharmacist Only Medicine.

Date of TGA approval: 25 May 2011.

Date of most recent amendment: 27 August 2013