

NEW ZEALAND DATA SHEET

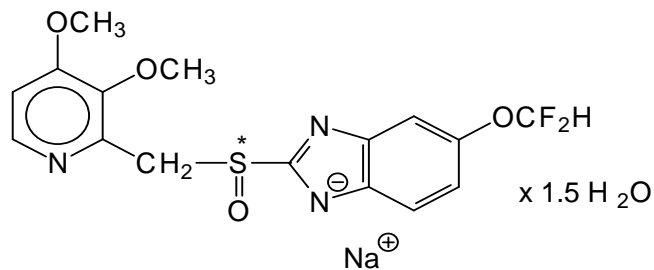
NAME OF MEDICINE

SOMAC[®] Heartburn Relief tablets

Non-proprietary name: Pantoprazole sodium (as pantoprazole sodium sesquihydrate)

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

The structure of pantoprazole sodium sesquihydrate is:



SOMAC Heartburn Relief enteric coated tablets contain 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole.

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

PRESENTATION

SOMAC Heartburn Relief 20 mg tablets are yellow and oval shaped, marked with the letter "P20" on one side.

In addition to pantoprazole sodium, these tablets also contain sodium carbonate anhydrous, mannitol, crospovidone, povidone, calcium stearate, hypromellose, titanium dioxide, iron oxide yellow (CI 77492), propylene glycol, methacrylic acid copolymer, polysorbate 80, sodium lauryl sulfate, triethyl citrate and Opacode Brown S-1-26514 printing ink.

USES

Actions

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-secreting 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 h, with a C_{max} of approximately 1.2 $\mu g/mL$. 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.

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 3-fold in patients with mild hepatic impairment and 5-fold in patients with severe hepatic impairment compared with healthy controls. Mean elimination half-life was 3.3 h in mild hepatic impairment and 6.0 h in severe hepatic impairment compared with 1.1 h in controls. The maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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

The slight increase in AUC and C_{max} in elderly volunteers compared with their younger counterparts is also not clinically relevant.

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 1.

Table 1: Efficacy of pantoprazole 20 mg in the treatment of symptomatic reflux (GORD)

Data Set	1 week			2 weeks		
	pantoprazole 20mg	Placebo	P	pantoprazole 20mg	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

Somac Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

DOSAGE AND ADMINISTRATION

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

Symptomatic GORD

The recommended dosage is one SOMAC Heartburn Relief 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 SOMAC Heartburn Relief 20 mg tablet per day, patients should be referred to their doctor.

Use in children

There are limited data currently available on the use of pantoprazole in children. SOMAC Heartburn Relief 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.

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**).

WARNINGS AND 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.
- They have had to take other medication for indigestion or heartburn continuously for four or more weeks in order to control their symptoms.
- They are being treated for symptomatic GORD and require SOMAC Heartburn Relief for more than 14 days.
- They have jaundice or severe hepatic impairment (e.g. cirrhosis), or
- They have any other significant medical condition.

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

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.

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.

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 breast feeding in humans. Therefore, pantoprazole should only be used during lactation if the benefits clearly outweigh the risks.

Use in children and adolescents under 18 years of age

To date there has been limited experience with treatment in children. SOMAC Heartburn Relief is not recommended for use in children and adolescents under 18 years of age.

Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines.

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 post-marketing surveillance. The following adverse reactions have been reported in patients receiving pantoprazole:

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 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 (blurred vision)

Very rare reports of conjunctivitis

INTERACTIONS

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**).

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 New Zealand National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

PHARMACEUTICAL PRECAUTIONS

SOMAC Heartburn Relief tablets should not be chewed or crushed but swallowed whole with a little water.

MEDICINE CLASSIFICATION

Restricted Medicine

PACKAGE QUANTITIES

SOMAC Heartburn Relief 20 mg tablets are available in blister packs of 2s, 7s and 14s.

FURTHER INFORMATION

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DATE OF PREPARATION

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