Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

Pharmacia&Upjohn

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SOM RA 002

26 August, 1997

Ms Angela Ludwig
Byk Gulden
Lomberg Chemische Fabrik GmbH
Postfach 10 03 10
78403 Konstanz
Germany

Dear Angela,

Re: Somac Approved Australian Product Information

In response to your fax dated 22 August 1997, please find enclosed a copy of the latest Product Information for Somac.

Kindest regards.
PHARMACIA & UPJOHN PTY LIMITED

Jane Freeman
Regulatory Affairs Associate

Enclos.

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Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

PRODUCT INFORMATION

SMC.TAB-PI
SOMall.001

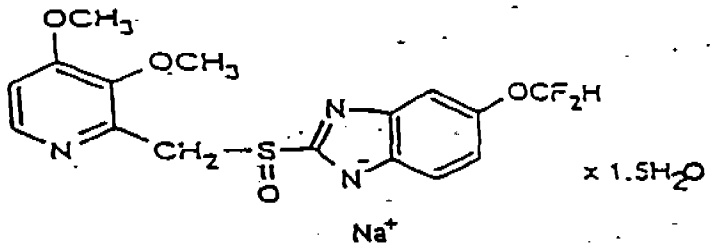
TRADE NAME: Somac

NAME OF THE DRUG:-
Pantoprazole sodium sesquihydrate.

DESCRIPTION:-

Pantoprazole 40 mg enteric coated tablets contain 45.1mg of pantoprazole sodium sesquihydrate. Chemical Name: ± sodium-[5-(Difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridinyl)-methyl] sulfinyl]-1H-benzimidazolide sesquihydrate. The molecular weight of pantoprazole, sodium salt x 1.5 H_2O is 432.4. Pantoprazole is a substituted benzimidazole which inhibits basal and stimulated gastric secretion. It is a white to off-white crystalline powder. Solubility is low at neutral pH and increases with increasing pH.

The structure of pantoprazole sodium sesquihydrate is:



PHARMACOLOGY:-

Pharmacodynamics

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H^+/K^+-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphenamide which binds to the H^+/K^+-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts it's 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.

The minimum effective dose of pantoprazole has not yet been determined and may be 30 mg/day.

Pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single 40 mg oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5h, with a Cmax of approximately 1.2µg/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 after both oral and intravenous administration.

Studies with pantoprazole in humans reveal no interaction with the cytochrome P450-system of the liver. There was no induction of the P450-system after chronic administration with antipyrine and no interactions were observed after concomitant administration of pantoprazole with either antipyrine, diazepam, theophylline or digoxin. Concomitant administration of warfarin has no influence on its effect on coagulation factors.

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 10h. Patients with a half-life of greater than 3.5h and with an apparent clearance of less than 2L/h/kg are considered to be slow metabolisers of pantoprazole.

In patients with liver cirrhosis changes in kinetics are not clinically relevant because of good tolerability and once daily administration. 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.

In patients with renal impairment (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.

INDICATIONS:-

For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion; duodenal ulcer, treatment up to 4 weeks; gastric ulcer and reflux oesophagitis (stage 2-3), treatment up to 8 weeks; gastrointestinal lesions refractory to H_2 blockers, treatment up to a maximum of 12 weeks; Zollinger-Ellison Syndrome.

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

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.

WARNINGS AND PRECAUTIONS:-

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

In the case of suspected gastric ulcer, malignancy of gastric carcinoma should be excluded as treatment could conceal the symptoms and may delay diagnosis.

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 5mg/kg/day in rats and 2.5mg/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.

Genotoxicity: it was noted that a minute amount of radioactivity was bound to rat hepatic DNA after treatment with 200mg/kg/day for 14 days. However, no distinct DNA-adduct has been detected. Additionally, pantoprazole did not demonstrate any clear genotoxic activity in a number of tests of mutagenicity and clastogenicity in bacterial and mammalian cells. Thus, there is no clear evidence of a genotoxic potential.

Carcinogenesis: a two year carcinogenicity study in rats showed an increase in the development of gastric carcinoid tumours after pantoprazole treatment at doses greater than 0.5mg/kg/day in females and greater than 5mg/kg/day in males. The development of gastric tumours is attributed to chronic elevation of serum gastrin levels with associated histopathological changes in the gastrointestinal system.

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

Treatment with pantoprazole at doses greater than 50mg/kg/day also increased the development of thyroid follicular cell adenomas in male and female rats. The mechanism behind thyroid tumour development is unknown, but may be secondary to hepatic thyroid hormone enzyme induction resulting in increased levels of the thyrotropic hormone, TSH.

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.

Thyroid: Thyroid tissue changes have been observed in the absence of an increase in thyroxine levels in long term studies (> 12 months) in rats and dogs. The significance of these effects to the short term treatment of humans is not known.

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.

Interactions with other drugs

No drug interactions have been reported so far. In studies with pantoprazole in humans, no interactions were observed after concomitant administration of pantoprazole with either antipyrine, diazepam, theophylline or digoxin. Concomitant administration of warfarin has no influence on its effect on coagulation factors.

Use in pregnancy - (Category B3)

Teratological studies in rats and rabbits gave no evidence of a teratogenic potential for pantoprazole. In rats, dose-dependent fetotoxic effects were noted; increased pre- and postnatal deaths (450mg/kg/day), reduced fetal weight and delayed skeletal ossification (150mg/kg/day), reduced pup

growth (15mg/kg/day). For the latter a no-effect dose was not established. Doses of 450mg/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 10mg/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 30mg/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.

ADVERSE REACTIONS:-

Somac is well tolerated. Most of the adverse events seen with treatment were of mild or moderate intensity. The following adverse events classified as possibly or definitely related to therapy, have been reported in clinical trials with an incidence of less than 1%:

Dermatological: pruritis rash.

Central and peripheral nervous system: headache, dizziness, dry mouth, increased sweating

Gastrointestinal: diarrhoea, nausea.

Biochemical: There were no consistent changes in any laboratory parameter. An increase in levels of SGPT however, was seen with an incidence of 0.2%.

Other: asthenia.

DOSAGE AND ADMINISTRATION:-

Pantoprazole should not be chewed or crushed but swallowed whole with a little water either before or during breakfast.

Duodenal Ulcer. Pantoprazole 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. Pantoprazole 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.

Reflux Oesophagitis (Stage 2 and 3) Pantoprazole 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, the dosage may be increased up to 80mg pantoprazole a day. Healing will usually be achieved within a further 4 weeks.

Lesions Refactory to H_2-Receptor Antagonists. Pantoprazole 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 dosages 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.

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 40mg is given.

Impaired Renal Function. The usual daily dose of 40 mg is 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 were administered i.v. or p.o. and were well tolerated. Normal intoxication procedures apply.

STORAGE:-

Store below 25°C.

PRESENTATION:-

40 mg tablets in PE bottles or blister packs of 14's ,28's and 30's. Also available in a hospital pack of 10 x 14's and a PE bottle of 5s. The tablets are marked with the letter "P40" on one side and blank on the reverse. *

POISON SCHEDULES:- S4.

DISTRIBUTOR:-

Pharmacia & Upjohn Pty Limited
59 Kirby Street, Rydalmere NSW 2116

TGA APPROVAL DATE:- 20th December 1994

* Please note changes in Product Information

Latest amendment date:-1 July 1997

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

Canada
Original Language

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

PRODUCT MONOGRAPH

PANTOLOC™
(Pantoprazole)

40 mg Enteric-Coated Tablets

H^+, K^+-ATPase Inhibitor

SOLVAY PHARMA
50 Ventura Drive, Scarborough, Ontario, Canada M1B 3L6

Date of preparation:
September 23, 1996

#048488

Revision Date:
February 6, 1997

PRODUCT MONOGRAPH

PANTOLOC™
(Pantoprazole)

40 mg Enteric Coated Tablets

THERAPEUTIC CLASSIFICATION
H^+, K^+-ATPase Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

PANTOLOC™ (pantoprazole) is a specific inhibitor of the gastric H+, K^+-ATPase enzyme (the proton pump) that is responsible for acid secretion by the parietal cells of the stomach.

Pantoprazole is a substituted benzimidazole that accumulates in the acidic environment of the parietal cells after absorption. Pantroprazole is then converted into the active form, a cyclic sulphenamide, which binds to the H^+, K^+-ATPase, thus inhibiting both the basal and stimulated gastric acid secretion. Pantoprazole exerts its effect in an acidic environment (pH < 3), and it is mostly inactive at higher pH. Its pharmacological and therapeutic effect is achieved in the acid-secretory parietal cells.

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

In clinical studies investigating intravenous (i.v.) and oral administration, pantoprazole inhibited pentagastrin-stimulated gastric acid secretion. With a daily oral dose of 40 mg, inhibition was 51% on Day 1 and 85% on Day 7. Basal 24-hour acidity was reduced by 37% and 98% on Days 1 and 7, respectively.

Fasting gastrin values increased during pantoprazole treatment, but in most cases the increase was only moderate.

Pantoprazole is absorbed rapidly following administration of a 40 mg enteric coated tablet. Its oral bioavailability compared to the i.v. dosage form is 77% and does not change upon multiple dosing. Following an oral dose of 40 mg, C_{max} is approximately 2.5 mg/L with a t_{max} of 2 to 3 h. The AUC is approximately 5 mg.h/L. Pantoprazole shows linear pharmacokinetics after both i.v. and oral administration. Therefore, elimination half-life, clearance and volume of distribution are independent of the dose. Concomitant intake of food has no influence on the bioavailability of pantoprazole.

Studies with pantoprazole in humans reveal no inhibition or activation of the cytochrome P450 (CYP 450) system of the liver.

Pantoprazole is 98% bound to serum proteins. It is almost completely metabolized in the liver. Renal elimination represents the major route of excretion (about 82%) for the metabolites of pantoprazole, the remaining metabolites are excreted in feces. The main metabolite in both the serum and urine is desmethylpantoprazole as a sulphate conjugate.

The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole (approximately 1 hour).

INDICATIONS AND CLINICAL USE

PANTOLOC™ (pantoprazole) is indicated for the treatment of conditions where a reduction of gastric acid secretion is required, such as the following:

- Duodenal ulcer
- Gastric ulcer
- Reflux esophagitis

Pantoprazole is not indicated for maintenance therapy. Until adequate long-term clinical data are available, pantoprazole should be prescribed only at the recommended dosage regimen (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

PANTOLOC™ (pantroprazole) is contraindicated in patients with a history of hypersensitivity to pantoprazole or to any constituents of the medication (see PHARMACEUTICAL INFORMATION). It is also contraindicated in patients with cirrhosis of the liver and in cases of severe liver disease (see PRECAUTIONS).

WARNINGS

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with PANTOLOC™ (pantroprazole) is instituted since treatment with pantoprazole may alleviate symptoms and delay diagnosis.

USE IN PREGNANCY

There are no adequate or well-controlled studies in pregnant women. Pantoprazole should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus (see also information under REPRODUCTION AND TERATOLOGY).

USE IN NURSING MOTHERS

It is not known whether pantoprazole is secreted in human milk. Pantoprazole should not be given to nursing mothers unless its use is believed to outweigh the potential risks to the infant.

USE IN CHILDREN

The safety and effectiveness of pantoprazole in children has not yet been established.

PRECAUTIONS

CARCINOGENICITY

Effects on long-term treatment relate to hypergastrinemia, possible enterochromaffin-like (ECL) cell hyperplasia and carcinoid formation in the stomach, adenomas and carcinomas in the liver and neoplastic changes in the thyroid.

In a 24 month carcinogenicity study, Sprague-Dawley (SD) rats were treated orally with PANTOLOC™ (pantoprazole) at 1.5, 5, 50, and 200 mg/kg/day. Pantoprazole produced gastric (ECL) cell hyperplasia and ECL cell carcinoid at doses of 50 mg/kg/day and above in males and at 0.5 mg/kg/day and above in females (first finding after 17 months treatment). The mechanism leading to the formation of gastric carcinoids is considered to be due to the elevated gastrin level occurring in the rat during chronic treatment. Similar observations have also been made after administration of other acid secretion inhibitors.

ECL-cell neoplasms were not observed in a 24 month carcinogenicity study in mice which were treated orally with pantoprazole at 5, 25, and 150 mg/kg/day. In clinical studies with treatment of 40 to 80 mg of pantoprazole for 1 year, ECL-cell density remained almost unchanged. (For further details, see TOXICOLOGY).

In the liver of the rat and female mouse, hepatocellular tumor formation was seen with pantoprazole. In rats, slightly increased liver tumor incidences were found at 50 mg/kg and above, and in the female mouse at 150 mg/kg. Hepatocellular tumors are common in mice, and the incidence found for the female 150 mg/kg group was within historical control

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

ranges for this strain. The liver tumor incidences in rats treated with 50 mg/kg and in the male rats treated with 200 mg/kg were also within historical control incidences for the SD rat. These tumors occurred late in the life of the animals and were primarily benign. The nongenotoxic mechanism of rodent liver tumor formation after prolonged treatment with pantoprazole is associated with enzyme induction leading to hepatomegaly and centrilobular hypertrophy and is characterized by tumor induction in low incidences at high doses only. Clinical pharmacological studies with pantoprazole show no induction or inhibition of human liver enzymes. Hepatocellular tumors in rodents exposed to high levels of pantoprazole are not indicative of human carcinogenic risk.

A slight increase in neoplastic changes of the thyroid was observed in rats receiving pantoprazole at 200 mg/kg/day. The incidences of these thyroid tumors were within the historical control ranges for this rat strain. The effect of pantoprazole on the thyroid is secondary to the effects on liver enzyme induction, leading to enhanced metabolism of thyroid hormones in the liver. As a consequence, increased TSH is produced, having a trophic effect on the thyroid gland. Clinical studies have demonstrated that neither liver enzyme induction nor changes in thyroid hormonal parameters occur in man after therapeutic doses of pantoprazole. (For further details, see TOXICOLOGY).

The clinical implication of the above observations made in animal studies is not known. Until adequate long term clinical data are available, pantoprazole should not be prescribed beyond the recommended dosage regimens.

USE IN THE ELDERLY

A slight increase in AUC (12%) and C_{max} (7%) for pantoprazole occurs in elderly volunteers when compared to younger volunteers. The daily dose used in elderly patients, as a rule, should not exceed the recommended dosage regimens.

HEPATIC INSUFFICIENCY

The half-life increased to between 7 and 9 h, the AUC increased by a factor of 5 to 7, and the C_{max} increased by a factor of 1.5 in patients with liver cirrhosis compared with healthy subjects. Pantoprazole should not be administered to patients with mild to moderate liver impairment unless the expected benefits outweigh the potential risks.

RENAL INSUFFICIENCY

No dose reduction is required when pantoprazole is administered to patients with impaired kidney function as the difference in AUCs between patients who are dialyzed and those who are not is 4%.

DRUG INTERACTIONS

Pantoprazole is metabolized in the liver via the CYP 450 system. Pharmacokinetic drug interaction studies in man did not demonstrate the inhibition of the oxidative metabolism of the drug. Pantoprazole does not interact with antipyrine, diazepam, phenytoin, nifedipine, theophylline, warfarin, digoxin, or oral contraceptives. Concomitant use of antacids or food consumption of food does not affect the pharmacokinetics of pantoprazole.

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

ADVERSE REACTIONS

Pantoprazole is well tolerated. Most adverse events have been mild and transient showing no consistent relationship with treatment. Adverse events have been recorded during controlled clinical investigations in 2082 patients exposed to pantoprazole.

The following adverse events (at a rate of at least 0.5%) have been reported in individuals receiving pantoprazole therapy (40 mg once daily) in controlled clinical situations: diarrhea (1.5%), headache (1.3%), dizziness (0.7%), pruritus (0.5%) and asthenia (0.3%). No unexpected adverse events have been reported with pantoprazole.

In addition, the following adverse events were reported in clinical trials:

Skin: Isolated cases of alopecia, acne, edema, maculopapular rash, urticaria, exfoliative dermatitis.

Central and Peripheral Nervous System: Rare cases of somnolence, insomnia; in isolated cases depression, vertigo, tremor, tinnitus, paresthesia, nervousness, photophobia.

Sensory Organs: Isolated cases of blurred vision.

Gastrointestinal: Rare cases of increased appetite, dry mouth, nausea, constipation, dyspeptic symptoms, acid eructation; in one case, gastrointestinal carcinoma.

Urogenital: Isolated cases of hematuria and impotence.

Hepatic: In rare cases, increased liver enzymes.

Hematologic: Isolated cases of eosinophilia.

Other: In isolated cases, malaise.

An extensive evaluation of clinical laboratory results has not revealed any clinically important changes during pantoprazole treatment (except for gastrin which increased to 1.5- fold after 4 to 8 weeks).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There are no known reports or experiences of PANTOLOC™ (pantoprazole) overdosage in man. Doses of up to 240 mg i.v. were administered and were well tolerated.

Treatment should be supportive and symptomatic.

DOSAGE AND ADMINISTRATION

DUODENAL ULCER

The recommended adult dose of pantoprazole for the oral treatment of duodenal ulcer is 40 mg given once daily in the morning. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional course of 2 weeks is recommended.

GASTRIC ULCER

The recommended adult oral dose of pantoprazole for the oral treatment of gastric ulcer is 40 mg given once daily in the morning. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional course of 4 weeks is recommended.

REFLUX ESOPHAGITIS

The recommended adult oral dose of pantoprazole is 40 mg, given once daily in the morning. In most patients, healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Pantoprazole is not indicated for maintenance therapy. Until adequate long term clinical data are available, pantoprazole should be prescribed only according to the recommended dosage regimens.

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

Pantoprazole is formulated as an enteric-coated tablet. A whole tablet should not be chewed or crushed, and should be swallowed with water in the morning either before, during or after breakfast.

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

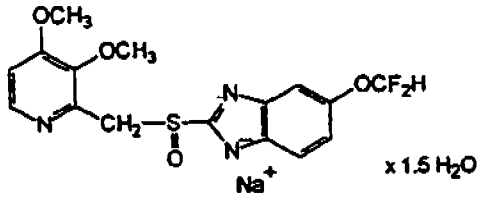
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: pantoprazole

Chemical Name: Sodium-[5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazolide sesquihydrate

Structural Formula:



Molecular Formula: $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$

Molecular Weight: 432.4

Physical Form: White to off-white powder

Solubility: Pantoprazole is freely soluble in ethanol, soluble in water, and slightly soluble in hexane.

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

pK_a:	3.92 pyridine; 8.19 benzimidazole
pH:	1% aqueous solution: 10.05 10% aqueous solution: 10.85
Melting point:	Because of gradual degradation of pantoprazole during heating, the melting point cannot be determined.

COMPOSITION

Active ingredient:	Each enteric-coated tablet contains 40 mg pantoprazole (45.1 mg pantoprazole sodium sesquihydrate).
Non-medicinal ingredients:	Calcium stearate, crospovidone, ferric oxide, mannitol, methylhydroxypropyl cellulose, poly(ethylacrylate, methacrylic acid), polysorbate 80, polyvidone, propylene glycol, anhydrous sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

Stability and Storage Conditions: Store at 15°C to 30°C in the recommended packaging.

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

Availability of Dosage Forms:

PANTOLOC™ (pantroprazole) is available as enteric-coated tablets for oral administration. Each yellow, oval, biconvex tablet marked P 40 on one side contains 40 mg pantoprazole (45.1 mg pantoprazole sodium sesquihydrate). Pantoprazole is available in bottles of 14 and 28 tablets.

Information for the Patient:

PANTOLOC (Pantoprazole) Enteric Coated Tablets

Please read the following information carefully.

This (booklet/leaflet/sheet) contains general information about Pantoloc. If you need more specific information, ask your doctor or pharmacist. It is important for you to follow carefully your doctor's instructions regarding how and when to take Pantoloc.

What is Pantoloc used for and how does it work?

Pantoloc is the brand name for the medication, pantoprazole.

Pantoloc is used to treat acid-related stomach problems such as stomach ulcers (also known as gastric ulcers), duodenal ulcers, and reflux esophagitis (a severe form of heartburn). Pantoloc works by reducing the amount of acid made in your stomach.