PRODUCT MONOGRAPH

[Pr] Dom-PANTOPRAZOLE

Pantoprazole Sodium for Injection

40 mg pantoprazole/vial
(pantoprazole as pantoprazole sodium sesquihydrate)

H^+, K^+-ATPase Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non medicinal Ingredients
Intravenous	Lyophilized powder for injection/40 mg	Sodium hydroxide and water

INDICATIONS AND CLINICAL USE

Dom-PANTOPRAZOLE (pantoprazole sodium for injection) is indicated for the short-term treatment (up to 7 days) of conditions where a rapid reduction of gastric acid secretion is required, such as the following:

- Reflux esophagitis, in hospitalized patients who cannot tolerate oral medication
- Pathological hypersecretion associated with Zollinger-Ellison Syndrome, in hospitalized patients who cannot tolerate oral medication

Geriatrics (> 65years of age):
No dosage adjustment is recommended based on age. The daily dose used in elderly patients, as a rule, should not exceed the recommended dosage regimens. See DETAILED PHARMACOLOGY.

Pediatrics:
The safety and effectiveness of pantoprazole sodium in children have not yet been established.

CONTRAINDICATIONS

Dom-PANTOPRAZOLE (pantoprazole sodium for injection) is contraindicated in patients who are hypersensitive to pantoprazole, substituted benzimidazoles, or to any ingredient in the formulation.

For a complete listing of ingredients, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

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, the possibility of malignancy should be excluded before therapy with Dom-PANTOPRAZOLE is instituted since treatment with pantoprazole sodium may alleviate symptoms and delay diagnosis.
Further investigation should be considered if symptoms persist despite adequate treatment.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see DRUG INTERACTIONS). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile*.

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis

Effects of long-term treatment include 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 the rat, the mechanism leading to the formation of gastric carcinoids is considered to be due to the elevated gastrin level occurring during chronic treatment. Similar observations have also been made after administration of other acid secretion inhibitors. (For further details, see TOXICOLOGY).

Short-term and long-term treatment with pantoprazole sodium in a limited number of patients up to 6 years have not resulted in any significant pathological changes in gastric oxyntic exocrine cells.

Endocrine and Metabolism

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

The chronic use of PPIs may lead to hypomagnesaemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Hepatic/Biliary/Pancreatic

The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg pantoprazole. In severe hepatically impaired patients with Zollinger-Ellison syndrome, doses of pantoprazole should be adjusted according to acid output measurements, and kept at a minimum effective dose. See ACTION & CLINICAL PHARMACOLOGY, Special Populations & Conditions.

Renal

The daily dose used in renal insufficient patients, as a rule, should not exceed the recommended dosage regimens. See ACTION & CLINICAL PHARMACOLOGY, Special Populations & Conditions.

Special Populations

Pregnant Women:

There are no adequate or well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity, the potential risk for humans is unknown. Dom-PANTOPRAZOLE should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus. See REPRODUCTION and TERATOLOGY.

Nursing Women:

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Pantoprazole sodium should not be given to nursing mothers unless its use is believed to outweigh the potential risks to the infant.

Pediatrics:

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

Geriatrics (> 65 years of age):
No dose adjustment is recommended based on age. The daily dose used in elderly patients, as a rule, should not exceed the recommended dosage regimens. See PHARMACOLOGY.

Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category (> 71 years of age) may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Monitoring and Laboratory Tests
Critically ill patients should be monitored carefully for any unexpected side effects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Pantoprazole sodium is well tolerated. Most adverse events have been mild and transient showing no consistent relationship with treatment.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In four controlled clinical trials involving 407 reflux esophagitis patients receiving pantoprazole sodium i.v. therapy (40 mg daily for 5-7 days, followed by oral administration up to a maximum of 7 weeks), the following adverse events were reported with a >1% frequency during the i.v. administration phase, and relation to drug administration could not be ruled out:

Table 1: Adverse reactions [>1% frequency; relation to administration of pantoprazole sodium i.v. 40 mg daily (5-7 days) could not be ruled out] reported in 4 controlled clinical trials (n=407)

Gastrointestinal disorders	
General complaints like abdominal pain, cramps, bloating and discomfort	1.97%
Constipation	1.22%
Diarrhea	1.97%
Loose/soft/Mushy stools	1.72%
Nausea/Nauseated	1.72%
Vomiting/Retching	1.97%
Nervous system disorders	
Headache/Headache dull	3.2%
General disorders and administration site conditions	
Injection site reactions (Inflammation, Bruises)	1.22%
Skin and subcutaneous tissue disorders	
Allergic skin reactions including Pruritus and Exanthema	1.22%

In two pantoprazole sodium i.v. studies in patients with Zollinger-Ellison syndrome, the following adverse events were reported most frequently and relation to drug administration (divided doses between 160 – 240 mg) could not be ruled out: Abdominal pain, Cough increased, Constipation, Diarrhea, Headache, Injection site reactions, Tachycardia, Taste perversion, and Twitching.

Post-Market Adverse Drug Reactions

The following events were reported in post-marketing use, and causal relation to intravenous pantoprazole sodium treatment could not be ruled out. As the events were reported spontaneously, no exact incidences can be provided, yet most of them occurred very rarely:

Interstitial nephritis; Stevens-Johnson Syndrome; Erythema multiforme; Toxic epidermal necrolysis (Lyell Syndrome); Photosensitivity; Hyponatraemia; Hypomagnesaemia; Hepatocellular injury; Jaundice; Hepatocellular failure; Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in the case of pre-existence). Hypokinesia, Anterior ischemic optic neuropathy; Pancreatitis; Increased salivation; Speech disorder; Elevated creatine phosphokinase; Rhabdomyolysis; Tinnitus

In addition the following identified adverse drug reactions have been reported in pantoprazole sodium clinical trials in any indication and in any dosage:

Common: Injection site thrombophlebitis.

Uncommon: Headache; Dizziness; Diarrhoea; Nausea/Vomiting; Abdominal distension and Bloating; Constipation; Dry mouth; Abdominal pain and discomfort; Rash/Exanthema/Eruption; Pruritis; Asthenia, Fatigue and Malaise; Liver enzymes increased (transaminases, γ-GT); Sleep disorders.

Rare: Agranulocytosis; Disturbances in vision/Blurred vision; Urticaria; Angioedema; Arthralgia; Myalgia; Hyperlipidaemias and Lipid increases (triglycerides, cholesterol); Weight changes; Body temperature increased; Oedema peripheral; Hypersensitivity (including Anaphylactic reactions and Anaphylactic shock); Bilirubin increased; Depression (and all aggravations), Taste disorder.

Very rare: Thrombocytopenia; Leukopenia; Pancytopenia; Disorientation (and all aggravations).

Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.

DRUG INTERACTIONS

Overview

Pantoprazole undergoes extensive hepatic metabolism via cytochrome P450-mediated oxidation. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways which include oxidation by CYP3A4. This is followed by sulphate conjugation via a Phase II reaction (non-saturable, non-cytochrome P450 dependent). No induction of the CYP 450 system by pantoprazole was observed during chronic administration with antipyrine as a marker. Because of the profound and long lasting inhibition of gastric acid secretion, pantoprazole sodium may interfere with the absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, itraconazole, posaconazole, erlotinib).

Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see WARNINGS AND PRECAUTIONS).

Drug-Drug Interactions

Pantoprazole sodium does not interact with carbamazepine, caffeine, diclofenac, naproxen, piroxicam, ethanol, glibenclamide, metoprolol, antipyrine, diazepam, phenytoin, nifedipine, theophylline, digoxin, oral contraceptives (levonorgestrel and ethinyl oestradiol), or cyclosporine. Concomitant use of antacids does not affect the pharmacokinetics of pantoprazole sodium.

Clinical studies have shown that there is no pharmacokinetic interaction between pantoprazole sodium and the following antibiotic combinations: metronidazole plus clarithromycin, metronidazole plus amoxicillin, amoxicillin plus clarithromycin.

Although no interaction during concomitant administration of warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in 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.

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Drug-Food Interactions
Consumption of food does not affect the pharmacokinetics (AUC and C_{max}) of pantoprazole sodium. See HUMAN PHARMACOLOGY.

Drug-Laboratory Interactions
There have been reports of false-positive results in urine screening tests for tetrahydrocannabinol (THC) in patients receiving most proton pump inhibitors, including pantoprazole. To some extent, a cross-reactivity of proton pump inhibitors to the THC assay in the OnTrak TesTcard™ 9 has been seen, though this may not be limited to this screening test. In order to verify positive urine screening results, a confirmatory method should be considered.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Patients should be switched to Dom-PANTOPRAZOLE (pantoprazole sodium) tablets when feasible. In switching, the same dose mg per mg should be administered. Daily doses of up to 272 mg pantoprazole i.v. were administered and were well tolerated. Pantoprazole sodium for injection has been administered for up to 7 days in clinical trials. Tolerance effects are not associated with the use of pantoprazole sodium for injection as demonstrated in clinical trials.

Recommended Dose and Dosage Adjustment

REFLUX ESOPHAGITIS
The recommended adult dose of Dom-PANTOPRAZOLE (pantoprazole sodium for injection) in patients with reflux esophagitis is 40 mg pantoprazole per day, administered either by slow intravenous injection over 2 to 5 minutes, or by intravenous infusion over 15 minutes.

PATHOLOGICAL HYPERSECRETION ASSOCIATED WITH ZOLLINGER-ELLISON SYNDROME
For patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, the recommended adult dose is 80 mg every 12 hours, administered by intravenous infusion over 15 minutes. Doses of 120 mg twice daily and 80 mg three times per day were also used to control acid output to below 10 mEq/h.

Patients should use the lowest dose and shortest duration of PPI therapy, appropriate to the condition being treated.

Administration
When preparing the intravenous infusion, polyvinyl chloride (PVC) and copolymer of ethylene and propylene (PAB) infusion bags, can be used.

40 mg intravenous injection: Inject 10 mL of physiological sodium chloride solution into the vial containing the dry substance. The resulting potency of the solution is 4 mg/mL of pantoprazole, and can be administered by slow injection over 2 to 5 minutes.

After preparation, the reconstituted (ready-to-use) solution for intravenous injection must be used within 24 hours of initial puncture of the stopper.

Reconstitution Medium	Administer within:
0.9% Sodium Chloride Injection , USP	24 hours

40 mg intravenous infusion: Prepare the 40 mg intravenous injection as described above. The ready-to-use solution should then be further diluted with 90 mL 0.9% Sodium Chloride Injection USP, or 90 mL of 5% Dextrose Injection. The resulting potency of the diluted solution is 0.4 mg/mL of pantoprazole, and can be administered by infusion over 15 minutes.

80 mg intravenous infusion: Two vials of Dom-PANTOPRAZOLE are required. Each vial should be reconstituted with 10 mL of physiological sodium chloride solution. The contents of the two vials should be further diluted together with 80 mL 0.9% Sodium Chloride Injection USP, or 80 mL 5% Dextrose Injection USP. The resulting potency of the diluted solution is 0.8 mg/mL of pantoprazole, and can be administered by infusion over 15 minutes.

When further diluting, the reconstituted solution in the vial must be diluted within 3 hours of the initial puncture of the stopper.

When further diluting with 0.9% sodium chloride injection USP for intravenous infusion, the solution must be administered within 21 hours.

When further diluting with 5% dextrose injection USP for intravenous infusion, the solution must be administered within 12 hours.

Diluent	Further dilute within:	Administer within:
0.9% Sodium Chloride Injection , USP	3 hours	21 hours following dilution
5% Dextrose Injection, USP	3 hours	12 hours following dilution

As with all parenteral admixtures, the reconstituted or further diluted solution should be examined for change in colour, precipitation, haziness or leakage. Discard unused portion.

Reconstitution:

Parenteral Products:

Dom-PANTOPRAZOLE should not be simultaneously administered through the same line with other intravenous solutions, and it is recommended that a dedicated line or a flushed line be used for administration. When a flushed intravenous line is used, it should be flushed before and after administration of Dom-PANTOPRAZOLE with either 0.9% sodium chloride injection USP, or 5% dextrose injection USP.

40 mg Intravenous Injection

0.9% Sodium Chloride Injection USP

Vial Size (mL)	Volume of Diluent (mL) to be added to the vial	Approximate	Nominal Concentration per mL
12	10	10	4 mg

For intravenous injection, a ready-to-use solution is prepared by injecting 10 mL of physiological sodium chloride solution into the vial containing the dry substance. The resulting potency is 4 mg/mL of pantoprazole.

40 mg Intravenous Infusion

Prepare as above; then,

1) 0.9% Sodium Chloride Injection USP

Volume of ready-to-use solution (mL)	Volume of Diluent (mL)	Approximate Available Volume (mL)	Nominal Concentration per mL
10	90	100	0.4 mg

2) 5% Dextrose Injection, USP

Volume of ready-to-use solution (mL)	Volume of Diluent (mL)	Approximate Available Volume (mL)	Nominal Concentration per mL
10	90	100	0.4 mg

For intravenous infusion of 40 mg: the solution is prepared by injecting 10 mL of physiological sodium chloride solution into the vial containing the dry substance. The ready-to-use solution should then be further diluted with 90 mL of 0.9% Sodium Chloride Injection USP, or 90 mL of 5% Dextrose Injection USP.

80 mg Intravenous Infusion

Two vials of Dom-PANTOPRAZOLE are required. Each vial should be reconstituted with 10 mL of physiological sodium solution.

1) 0.9% Sodium Chloride Injection, USP

Volume of ready-to-use solution (mL)	Volume of Diluent (mL)	Approximate Available Volume (mL)	Nominal Concentration per mL
20	80	100	0.8 mg

2) 5% Dextrose Injection, USP

Volume of ready-to-use solution (mL)	Volume of Diluent (mL)	Approximate Available Volume (mL)	Nominal Concentration per mL
20	80	100	0.8 mg

For intravenous infusion of 80 mg: The two ready-to-use solutions should then be further diluted together with 80 mL 0.9% sodium chloride injection USP, or 80 mL of 5% dextrose injection USP.

OVERDOSAGE

Some reports of overdosage with pantoprazole sodium have been received. No consistent symptom profile was observed after ingestion of high doses of pantoprazole sodium. Daily doses of up to 272 mg pantoprazole sodium i.v., and single doses of 240 mg administered over 2 minutes, have been administered and were well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialyzable. In the case of overdosage with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

For management of a suspected drug overdosage, contact your regional Poison Control Center immediately

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pantoprazole sodium for injection 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 sodium is a substituted benzimidazole that accumulates in the acidic environment of the parietal cells after absorption. Pantoprazole sodium is then converted into the active form, a cyclic sulphenamide, which binds selectively to the proton translocating region of the H^+, K^+-

ATPase, thus inhibiting both the basal and stimulated gastric acid secretion, in a dose dependent manner. Pantoprazole sodium 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. As pantoprazole action is distal to the receptor levels, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Fasting gastrin values increased during pantoprazole treatment, but in most cases the increase was only moderate. An extensive evaluation of clinical laboratory results has not revealed any clinically important changes during pantoprazole sodium treatment (except for gastrin which increased to 1.5-fold after 4 to 8 weeks).

Pharmacodynamics

In clinical studies investigating intravenous (i.v.) and oral administration, pantoprazole sodium 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.

Pharmacokinetics

Absorption: 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 µg/mL with a T_{max} of 2 to 3 hours. The AUC is approximately 5 µg.h/mL. There is no food effect on AUC (bioavailability) and C_{max}.

Distribution: Pantoprazole is 98% bound to serum proteins. Elimination half-life, clearance and volume of distribution are independent of the dose.

Metabolism: Pantoprazole is almost completely metabolized in the liver. Pantoprazole sodium is mainly metabolized by CYP2C19 and to a minor extent CYPs 3A4. Studies with pantoprazole in humans reveal no inhibition or activation of the cytochrome P450 (CYP 450) system of the liver.

Excretion: 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).

Pantoprazole shows linear pharmacokinetics, i.e., AUC and C_{max} increase in proportion with the dose within the dose-range of 10 to 80 mg after both i.v. and oral administration. Elimination half-life, clearance and volume of distribution are considered to be dose-independent. Following repeated i.v. or oral administration, the AUC of pantoprazole was similar to a single dose.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of pantoprazole in children have not yet been established.

Geriatrics: After repeated intravenous administration in healthy elderly subjects, total serum clearance of pantoprazole sodium was similar to that observed in healthy younger subjects. No dosage adjustment is recommended based on age. 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 following administration of 40 mg pantoprazole. Similarly, following administration of a 20 mg dose, the AUC increased by a factor of 5.5 and the C_{max} increased by a factor of 1.3 in patients with severe liver cirrhosis compared with healthy subjects. Considering the linear pharmacokinetics of pantoprazole, there is an increase in AUC by a factor of 2.75 in patients with severe liver cirrhosis following administration of a 20 mg dose compared to healthy volunteers following administration of a 40 mg dose. Thus, the daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg pantoprazole.

In severe hepatically impaired patients with Zollinger-Ellison syndrome, doses of pantoprazole should be adjusted according to acid output measurements, and kept at a minimum effective dose.

Renal Insufficiency: In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole sodium were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

STORAGE AND STABILITY

Store between 15ºC and 30ºC and protect from light.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

10 mL vials: Each vial contains 40 mg pantoprazole (equivalent to 42.3 mg pantoprazole sodium and to 45.1 mg pantoprazole sesquihydrate) as a lyophilized powder.

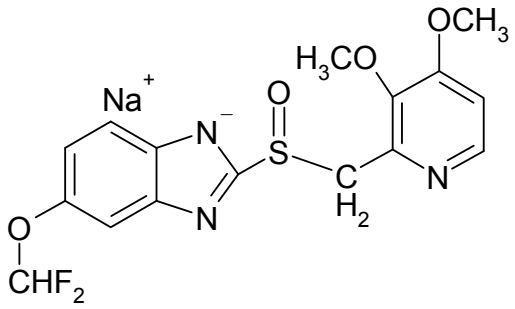
Non-medicinal ingredients: sodium hydroxide and water

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Pantoprazole Sodium
Common name:	pantoprazole sodium sesquihydrate
Chemical name:	5-(difluromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole sodium salt sesquihydrate
Molecular formula:	Racemate $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$
Relative molecular mass:	432 g/mol
Molecular formula of pantoprazole base:	$C_{16}H_{15}F_2N_3O_4S$
Molecular mass of pantoprazole base:	383.4 g/mol
Structural formula:	



Physicochemical properties:

Physical description:	White to off-white powder
Solubilities:	Pantoprazole sodium is freely soluble in ethanol and water, and practically insoluble in hexane.
pH:	1% aqueous solution: 10.05 10% aqueous solution: 10.85
pKa:	3.94 pyridine; 8.23 benzimidazole

Melting Point:	Because of gradual degradation of pantoprazole sodium during heating, the melting point cannot be determined.

CLINICAL TRIALS

Studies in patients with GERD

Endoscopically diagnosed patients with moderate or severe gastro-esophageal reflux disease (GERD stage II and III, respectively, Savary-Miller classification) were studied in an open label-historical control trial design to investigate the efficacy and safety of an intravenous-oral regimen of pantoprazole sodium. Patients were treated once daily with 40 mg pantoprazole sodium, which was administered as an intravenous injection for the initial 5-7 consecutive days, then as a tablet for up to 8 weeks. The efficacy parameters were complete healing of lesions evaluated endoscopically after 4 and 8 weeks of treatment, and relief of symptoms assessed after 2 and 4 weeks of treatment. Table 2 shows the results of this study. Pantoprazole sodium applied as an intravenous-oral regimen to patients with GERD led to fast resolution of symptoms and high healing rates.

For patients, unable to take oral medications, this regimen offers safe and reliable gastric acid suppression and allows the possibility of changing between the oral and intravenous administration without the need for dose adjustment.

Table 2: Efficacy results in patients with moderate or severe GERD (stage II or III)

Efficacy parameter	2 weeks	4 weeks	8 weeks
Healing of esophageal lesions, per protocol (n=98)	Not evaluated	87%	95%
Healing of esophageal lesions, ITT (n=110)	Not evaluated	77%	85%
Relief of heartburn, per protocol (n=95)	97%	99%	Not evaluated
Relief of acid regurgitation, per protocol (n=93)	98%	98%	Not evaluated
Relief of pain on swallowing, per protocol (n=37)	100%	100%	Not evaluated

Studies in patients with ZES

Two studies measured the pharmacodynamic effects of 6 days treatment with pantoprazole sodium for injection in patients with Zollinger-Ellison syndrome (with and without multiple endocrine neoplasia type I). In one of these studies in 21 patients, an initial treatment with pantoprazole sodium for injection reduced acid output to the target level ($\leq$10 mEq/h or $\leq$5 mEq/h in patients who have undergone surgery) in all 21 patients, and significantly reduced acid concentration and the volume of gastric secretions. Target levels were achieved within 1 hour of drug administration.

In the other study of 14 patients with Zollinger-Ellison syndrome, treatment was switched from an oral proton pump inhibitor to pantoprazole sodium for injection. Pantoprazole sodium for injection maintained or improved control of gastric acid secretion. Therefore patients can be switched from oral PPI therapy to pantoprazole i.v. without losing control of acid output.

In both studies, basal acid secretion was maintained well below target levels (≤10 mEq/h or ≤5 mEq/h in patients who have undergone surgery) in 34 of 35 patients with a daily dose of 160 mg (80 mg q12h) or 240 mg (120 mg q12h or 80 mg q8h) pantoprazole sodium for injection. Once gastric acid secretion was controlled, there was no evidence of tolerance. In both studies, doses were adjusted to the individual patient need, but gastric acid secretion was controlled in greater than 80% of patients with a starting regimen of 80 mg every 12 hours. In these clinical studies, pantoprazole sodium for injection was well-tolerated at all doses.

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacodynamics:

In vivo, pantoprazole produced marked and long-lasting inhibition of basal and stimulated gastric acid secretion with median effective dose (ED_{50}) values ranging from 0.2 -2.4 mg/kg in rats and dogs. In addition to the administration of single doses, pantoprazole has been tested upon repeated oral administration (e.g. during 24-h pH-metry in dogs performed under pentagastrin stimulation). While a dose of 1.2 mg/kg did not significantly elevate pH on Day 1, pH rose to values between 4 and 7 after a 5-day dosing regimen. This effect was no longer observed 18 hours after the last drug administration. In various gastric ulcer models in the rat, pantoprazole showed antiulcer activity.

In parallel to the profound inhibition of gastric acid secretion, pantoprazole induced a dose-dependent increase in serum gastrin levels up to values above 1000 pg/mL from a control level of about 100 pg/mL. As a consequence of persisting hypergastrinemia in rats after high/doses of pantoprazole, hyperplastic changes were observed in the fundic mucosa with an increased density of enterochromaffin-like (ECL) cells. These changes were reversible during drug-free recovery periods.

In a battery of standard high-dose pharmacology tests, no influence of pantoprazole was detected on the central and peripheral nervous system. In conscious dogs as well as anaesthetized cats receiving single i.v. doses up to 10 mg/kg pantoprazole, no consistent changes with respect to respiratory rate, ECG, EEG, blood pressure and heart rate were observed. Higher doses led to modest and transient reductions in blood pressure and variable changes in heart rate. No influence of pantoprazole was found on renal function and on autonomic functions, such as pancreatic and bile secretion, gastrointestinal motility and body temperature.

No consistent changes in the effects of ethanol, pentobarbitone, or hexobarbitone were induced by pantoprazole; only doses over 300 mg/kg prolonged the effects of diazepam.

Pharmacokinetics:

Absorption and Distribution

Pantoprazole is absorbed rapidly in both rat and dog. Peak plasma levels are attained within 15 to 20 minutes in the rat and after about 1 hour in the dog. Oral bioavailability is 33% in the rat and 49 % in the dog. Following absorption, autoradiography and quantitative tissue distribution experiments have shown that pantoprazole is rapidly distributed to extravascular sites. Following administration of pantoprazole, distribution of radioactivity in the blood and most organs is

found to be uniform initially. After 16 hours, radiolabelled pantoprazole is predominantly detected in the stomach wall. After 48 hours, all the administered radioactivity is found to have been excreted. Penetration of the blood-brain barrier by radiolabelled pantoprazole is very low. Protein binding in the rat and dog is 95% and 86%, respectively.

Metabolism and Excretion
Pantoprazole is extensively metabolized. Oxidations and reductions at different sites of the molecule, together with Phase II reactions (sulphation and glucuronidation) and combinations thereof result in the formation of various metabolites. In rats and dogs, 29-33% of the dose is excreted as urinary metabolites, and the remainder as biliary/fecal metabolites. Almost no parent compound can be found in the excreta.

Mammoglandular passage and transplacental transport has been investigated in the rat using radiolabelled pantoprazole. A maximum of 0.23% of the administered dose is excreted in the milk. Radioactivity penetrates the placenta with 0.1-0.2% of the dose /g fetal tissue on the first day after oral administration.

HUMAN PHARMACOLOGY
Pharmacodynamics:
Pantoprazole is a potent inhibitor of gastric acid secretion. This was demonstrated by use of a gastric acid aspiration technique as well as by continuous intragastric pH monitoring. Using the aspiration technique it was also shown that pantoprazole caused a dose-dependent reduction of secreted gastric acid volume.

Table 3: Percent inhibition of pentagastrin-stimulated acid output (PSAO) in healthy volunteers following single oral doses of Pantoprazole vs. placebo during 4 to7 hours post dosing.

Dose	Mean %Inhibition of PSAO
6 mg	13%
10 mg	24%
20 mg	27%
40 mg	42%
60 mg	54%
80 mg	80%
100 mg	82%

With 40 mg administered orally, effective inhibition of gastric acid secretion was achieved. Pantoprazole 40 mg was significantly superior to standard H2-blocker therapy (300 mg ranitidine at night) with regard to median 24-hour and daytime pH; however, not for nighttime measurements.

Table 4: Effects of one week oral treatment in healthy volunteers with placebo, Pantoprazole 40 mg in the morning, and standard ranitidine therapy with 300 mg in the evening

Time of Day	Median pH		
	Placebo	Pantoprazole 40 mg	Ranitidine 300 mg
08.00-08.00 (24h)	1.6	4.2*	2.7
08.00-22.00 (Daytime)	1.8	4.4*	2.0
22.00-08.00 (Nighttime)	1.3	3.1	3,7

* $p<0.05$ vs ranitidine

Increasing the once daily dose from 40 mg to 80 mg pantoprazole did not result in a significantly higher median 24-hour pH.

Table 5: Effect of oral Pantoprazole in healthy volunteers on median 24-hour pH on Day 7 (40 vs 80 mg).

40 mg	80 mg	
3.8	3.85	n.s.

n.s. = not significant

Hence, once daily administration of 40 mg pantoprazole should be sufficient for the treatment of most patients with acid-related diseases.

Pharmacokinetics:

The absolute bioavailability of the pantoprazole tablet is 77%. Maximum serum concentrations of pantoprazole are reached within approximately 2.5 hours after oral intake. Following a dose of 40 mg pantoprazole, mean maximum serum concentrations of approximately 2 µg/mL and 3 µg/mL are reached after 2 to 3 hours. There is no food effect on AUC (bioavailability) and C_{max}. However, time to reach maximum serum concentrations is slightly increased when the drug is given together with a high caloric breakfast. Taking into account the long duration of action of pantoprazole, which by far exceeds the time period over which serum concentrations are measurable, this observed variation in t_{max} is considered to be of no clinical importance.

Pantoprazole is approximately 98% bound to serum protein.

Despite its relatively short elimination half-life of approximately 1 hour, the antisecretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life. This means that there is no direct correlation between the serum concentrations and the pharmacodynamic action.

Morning administration of pantoprazole was significantly superior to evening dosing with regard to 24-hour intragastric pH, hence morning dosing should be recommended for the treatment of patients. Since the intake of the drug before a breakfast did not influence C_{max} and AUC, which

characterize rate and extent of absorption, no specific requirements for intake of pantoprazole in relation to breakfast are necessary.

Pantoprazole undergoes metabolic transformation in the liver via the cytochrome P450 system mainly by enzyme CYP2C19 and to a minor extent CYP3A4. Approximately 82% of the oral dose is removed by renal excretion, and the remainder via feces. The main serum metabolites (M1-M3) are sulphate conjugates formed after demethylation at the pyridine moiety, the sulphoxide group being either retained (M2, main metabolite), or oxidized to a sulphone (M1), or reduced to a sulphide (M3). These metabolites also occur in the urine (main metabolite M2). Conjugates with glucuronic acid are also found in the urine.

TOXICOLOGY

Acute toxicity
In acute toxicity studies in mice the mean lethal dose (LD_{50}) values for pantoprazole were found to be around 390 mg/kg body weight for i.v. administration and around 700 mg/kg body weight for oral administration.

In the rat the corresponding values were around 250 mg/kg for i.v. administration and > 1000 mg/kg for oral administration.

Acute toxicity studies were conducted on B8810-044, the major degradation product of pantoprazole. The approximate LD_{50} values for mice (119-167 mg/kg) and rats (73-82 mg/kg) were lower than those for pantoprazole itself, after intravenous injection, but the toxic symptoms were similar to those noted for the drug. A 4-week repeat dose study was also conducted using this degradation product using the intravenous route in rats. Rats received 5 and 25 mg of B8810-044/kg, while a comparison group received 25 mg/kg of pantoprazole. Muscle twitches were observed immediately after injection in rats receiving 25 mg/kg of the degradation product, but not in the pantoprazole-treated animals. Otherwise the compounds were comparable.

Table 6: Acute toxicity studies of Pantoprazole

SPECIES	SEX	ROUTE	ca, LD_{50}* (mg/kg)
Mouse	M	p.o.	>1000
	F	p.o.	747
Mouse	M	i.v.	399
	F	i.v.	395
Rat	M	p.o.	1343
	F	p.o.	1037
Rat	M	i.v.	330
	F	i.v.	343
Dog	M/F	p.o.	300-1000**
	M/F	i.v.	150-300

* Doses refer to the sodium salt administered in solution
** sodium salt as dry powder in gelatine capsules

The symptoms seen after lethal oral or i.v. doses were similar in rats and mice: the animals displayed ataxia, reduced activity, hypothermia and prostration. Surviving animals recovered

uneventfully. Salivation, tremor, lethargy, prostration and coma were seen in dogs at lethal oral doses, with death occurring on the following day. Ataxia, tremor and a prone position were noted at sublethal oral and i.v. doses, but the survivors recovered quickly and appeared fully normal after the 2-week observation period.

Local tolerance
Local tolerance studies of pantoprazole lyophilisate after a single intravenous, paravenous or intra-arterial injection in the rabbit or a single intramuscular injection in the rat showed no evidence of toxicity.

Single dose irritation studies in rabbits showed comparable results between i.v. formulations with and without edetate disodium dihydrate.

Chronic toxicity
Daily oral doses of pantoprazole in the 1- and 6-month SD rat repeated-dose studies were 1, 5,20, and 500 mg/kg and 0.8, 4, 16 and 320 mg/kg, respectively; doses for the 1 month rat pantoprazole i.v. study were 1, 5, and 30 mg/kg.

A 12-month toxicity study in SD rats was conducted using daily oral doses of 5, 50, and 300 mg/kg. Daily oral doses in the 1- and 6 month (beagle) dog studies were 7.5, 15, 30, and 100 mg/kg and 5, 15, 30, and 60 mg/kg respectively. In the 12-month oral study in dogs, 2.5, 15, and 60 mg/kg were administered daily.

Hypergastrinemia was dose-related and was observed at all doses investigated in the studies mentioned above, but was reversible upon cessation of treatment. Drug-related effects on the stomach included increased stomach weights and morphologic changes of the mucosal. After intravenous administration, the only morphologic change seen in the rat stomach was an increased incidence of eosinophilic chief cells in the glandular stomach. In the 6-month rat study, increased stomach weight and some cellular changes were detected at all doses. In the 1-month rat study, gastric changes were detected at 5 mg/kg but not at 1 mg/kg. In dogs, increased stomach weight was observed at all doses studied. There were no gastric cellular changes detected at oral doses of 7.5 or 5 mg/kg in the 1- and 6-month dog studies, respectively. In both species, most gastric effects were reversible after a 4- or 8-week recovery period. Hypergastrinemia and gastric changes were considered to be the consequence of the pharmacological action of the compound, namely prolonged and profound inhibition of acid secretion.

Increased liver weight in the rat experiments was considered to be a consequence of the induction of hepatic drug metabolizing systems and was found to be associated with centrilobular hepatocellular hypertrophy at 320 mg/kg in the 6-month study and at 50 and 300 mg/kg after 12 months of treatment. Increased liver weights were also detected at a dose of 16 mg/kg in male rats in the 6-month study and at 500 mg/kg, but not 20 mg/kg, in the 1-month study. Increased liver weight was noted in male dogs of all dose groups in the 1-month study, though only at 100 mg/kg in females on the same study. Both males and females had increased liver weights after 6 months administration of 30 or 60 mg/kg, but not as 15 mg/kg. In the 12-month study, liver weights were increased only in the female dogs dosed with 60 mg/kg. There were no hepatic lesions that correlated with increased liver weight in the dog studies. In dogs,

the increase in liver weight was attributed to an activation of hepatic drug metabolizing systems as mentioned for rats.

Thyroid activation in animal experiments is due to the rapid metabolization of thyroid hormones in the liver and has been described in a similar form for other drugs. Thyroid weights were increased in both sexes at 500 mg/kg in the 1-month rat study and at 320 mg/kg in the rat 6-month study. Thyroid follicular cell hypertrophy was noted in females at these doses, in rats treated with 50 and 300 mg/kg in the 12 month study and also in a few females at 16 mg/kg in the 6 month study. There were no thyroid effects in rats at or below an oral dose of 5 mg/kg even after 1 year. In the dog, no effects were seen on the thyroid after 4 weeks. Only slight, but not dose-dependent, increases in thyroid weights were seen after 6 months, but no changes were observed histologically. In the 12 month study, the relative thyroid weights in the 60 mg/kg group were only slightly higher than those of the control dogs, and changes were detected histologically in only a few animals under 15 and 60 mg/kg. In both species, changes were reversible.

Increased serum cholesterol values were noted in all groups in the 6- and 12 month dog studies and in all groups in the 12 month rat study. The increases were slight and were reversible after cessation of treatment.

In dog studies, oral doses of pantoprazole of 15 mg/kg or above caused a transient pulmonary edema in a proportion of naive dogs during the first week of drug administration. Pulmonary edema caused death in a few dogs after repeated oral doses of 15 mg/kg or above. There is strong evidence that the pulmonary toxicity is due to a thiol metabolite which does not occur in man. No evidence of pulmonary edema was detected in dogs at an oral dose of 7.5 mg/kg nor at 60 mg/kg when administered daily for 6 or 12 months after a 1 week dose escalation phase.

Carcinogenicity
Three carcinogenicity studies have been conducted:

- A 24 month oral study was conducted at doses of 0.5, 5, 50 and 200 mg/kg/day in SD rat.
- A 24 month oral study was conducted at doses of 5, 15 and 50 mg/kg/day in Fischer-344 rats.
- A 24 month oral study was conducted at doses of 5, 25 and 150 mg/kg/day in B6C3F1 mouse.

Pantoprazole, dissolved in distilled water, was administered once a day by oral gavage to groups of 50 male and 50 female B6C3F1 mice at doses of 5, 25, or 150 mg/kg. An identical control group was dosed with distilled water (pH 10), while a second identical control group received no treatment at all. In the first rat study, pantoprazole was administered once a day by oral gavage to groups of 70 male and 70 female SD rats at doses of 0.5, 5, 50, and 200 mg/kg. A control group of 70 males and 70 females received the vehicle. In the second rat study, pantoprazole was administered once a day by oral gavage to groups of 50 male and 50 female Fischer-344 rats at doses of 5, 15, and 50 mg/kg. A control group of 50 males and 50 females received the vehicle, while another group remained untreated.

In the first 2 year carcinogenicity study in rats, which corresponds to a lifetime treatment for rats, neuroendocrine neoplasms were found in the stomach at doses of 50 mg/kg/day and above in males and at 0.5 mg/kg/day and above in females. Tumor formation occurred late in the life of

the animals (only after 17 months treatment), whereas no tumors were found in rats treated with an even higher dose for 1 year. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated, and it is considered to be due to high levels of serum gastrin observed in the rat during chronic treatment. In the second rat carcinogenicity study, neuroendocrine cell tumors in the stomach were found in all treated female groups and in the male 15 and 50 mg/kg groups.

ECL-cell neoplasms were not observed in either the carcinogenicity study in the mouse (24 months) or in the chronic studies in the dog. In clinical studies, where pantoprazole was administered at doses up to 80 mg, ECL-cell density remained almost unchanged.

Microscopy of the rat (first carcinogenicity study) and mouse tissues gave evidence for an increase in liver tumors. In the rat experiment, the incidence of benign liver tumors in the 50 and 200 mg/kg groups and the incidence of hepatocellular carcinoma was increased in the males and females of the 200 mg/kg group. There was a slightly higher incidence of hepatocellular adenomas and carcinomas in the female mice of the 150 mg/kg group than in either of the 2 control groups. Other changes in the liver morphology were present as well. Centrilobular hepatocellular hypertrophy increased in incidence and severity with increasing dose, and hepatocellular necrosis was increased in the highest dose in the rat and mouse studies. Hepatocellular tumors are common in mice, and the incidence found for the female 150 mg/kg group was within historical control 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 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. As pantoprazole acts in a similar fashion to phenobarbital, causing reversible centrilobular hepatocellular hypertrophy and enzyme induction in short-term studies, it is probable that the mechanism of action for induction of the liver tumors seen in long-term rodent studies is also the same. Hepatocellular tumors at high doses in rodents 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 tumors were within the historical control ranges for this rat strain. No thyroid neoplasms were observed in the 12-month study. The no-effect dose for both male and female rats is 50 mg/kg, which is 100 times the most commonly used human dose (i.e. 40 mg). The effect of pantoprazole on the thyroid is secondary to the effects on liver enzyme induction, which lead to enhanced metabolism of thyroid hormones in the liver. As a consequence, increased TSH is produced, which has 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.

Tumors induced in rats and mice by pantoprazole were the result of nongenotoxic mechanisms which are not relevant to humans. Tumors were induced in rodents at dosages that provide higher exposure than with human therapeutic use. Based on kinetic data, the exposure to pantoprazole in rats receiving 200 mg/kg was 22.5 times higher than that found in humans

receiving 40 mg oral doses. In mice receiving 150 mg/kg, exposure to pantoprazole was 2.5 times higher than that in humans.

Mutagenicity
Pantoprazole was studied in several mutagenicity studies: Pantoprazole was found negative in the Ames test, an *in vivo* chromosome aberration assay in rat bone marrow, a mouse lymphoma test, two gene mutation tests in Chinese hamster ovary cells *in vitro,* and two micronucleus tests in mice *in vivo.* Pantoprazole was found positive in three of four chromosome aberration assays in human lymphocytes *in vitro.* The *in vitro* tests were conducted both in the presence and absence of metabolic activation. The potential of pantoprazole to induce DNA repair synthesis was tested negative in an *in vitro* assay using rat hepatocytes. In addition, a rat liver DNA covalent binding assay showed no biologically relevant binding of pantoprazole to DNA.

In addition, two *in vitro* cell transformation assays using different cell types were performed to aid in the interpretation of the rodent carcinogenicity studies; in neither test did pantoprazole enhance the morphologic transformation of the cell types used.

A bacterial mutation assay conducted with the degradation product B8810-044, gave no indication of a mutagenic potential.

Reproduction and teratology
Pantoprazole was not teratogenic to rats or rabbits at doses up to 450 and 40 mg/kg/day (gavage), 20 and 15 mg/kg/day (i.v. injection), respectively.

Treatment of male rats with pantoprazole up to 500 mg/kg p.o. for 127 days did not affect fertility. Treatment of pregnant rats induced dose-dependent fetotoxic effects: increased pre- and postnatal deaths (450 mg/kg/day), reduced fetal weight and delayed skeletal ossification (150 mg/kg/day), and reduced pup weight (15 mg/kg/day). These results may be explained by maternal toxicity of pantoprazole at high dose and/or placental transfer of pantoprazole.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the fetus is increased shortly before birth regardless of the route of administration.

In humans, there are no adequate or well-controlled studies with the use of pantoprazole during pregnancy.

REFERENCES

1. Gugler R., Hartmann M., Rudi J., Bliesath H., Brod I., Klotz U., Huber R., Steinijans V.W., Bliesath H., Wurst W., Klotz U.; *Lack of interaction of pantoprazole and diazepam in man;* Br J Pharmacol 1996; 42(2):249-252.

2. Hanauer G., Graf U., Meissner T.; *In vivo cytochrome P-450 interactions of the newly developed H^+, K^+-ATPase inhibitor Pantoprazole (BY1023/SK&F96022) compared to other antiulcer drugs;* Meth. Find. Exp. C. in Pharmacol. 1991; 13(1):63-67.

3. Hannan A., Well, J.; *Effects of oral Pantoprazole on 24 hour intragastric acidity and plasma gastrin profiles;* Aliment. Pharmacol. Ther. 1992; 6:373-380.

4. Hartmann M., Theị U., Bliesath H., Kuhn I., Lühmann R., Huber R., Wurst W., Postius S., Lücker P.; *24 h intragastric pH following oral intake of Pantoprazole and omeprazole;* Hellenic J. Gastroenterol. 1992; 5(suppl.):112 (A No. 451).

5. Huber R, Kohl B, Sachs G, Senn-Bilfinger J, Simon WA, Sturm E. *Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole,* Aliment Pharmacol Ther 1995;9;363-378.

6. Huber R, Hartmann, M, Bliesath H, Lühmann R, Steinijans V W, Zech K. *Pharmacokinetics of pantoprazole in man.* Internal J Clin Pharmacol Therap 1996;34:185-194.

7. Kohl B. et al.; *(H^+,K^+)-ATPase inhibiting - 2-[(2-pyridylmethyl)suftinyl] benzimidazoles. A novel series of dimethoxypyridyl-substituted inhibitors with enhanced selectivity. The selection of Pantoprazole as a clinical candidate;* J. Medicinal Chem. 1992; 35:1049-1057.

8. Lew EA, Pisegna JR, Starr JA, Soffer EF, Forsmark C, Modlin IM, Walsh FH, Beg M, Bochenek W, Metz DC. *Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger-Ellison syndrome.* Gastroenterology 2000; 118: 696-704.

9. Müller P., Simon B., Khalil H., Lühmann R., Leucht U., Schneider A.; *Dose-range finding study with the proton pump inhibitor Pantoprazole in acute duodenal ulcer patients; Z.* Gastroenterol. 1992; 30:771-775.

10. Pue M.A., Laroche J., Meineke I., de Mey C.; *Pharmacokinetics of Pantoprazole following single intravenous and oral administration to healthy male subjects;* Eur. J. Clin. Pharmacol. 1993; 44:575-578.

11. Koop H, Schepp W, Dammann HG, Schneider A, Lühmann R, and Classen M. *Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis;* J Clin Gastroenterol 1995; 20 (3): 192-5.

12. Sachs G.; *Gastric H, K-ATPase as therapeutic target;* Ann. Rev. Pharmacol. Toxicol. 1988; 28:269-284.

13. Schulz H.-U., Hartmann M., Steinijans, V. W., Huber R., Luhrmann B., Bliesath H., Wurst *W.; Lack of influence of pantoprazole on the disposition kinetics of theophylline in man;* Int J. Clin. Pharmacol. Ther. Toxicol. 1991; 9:369-375.

14. Simon B., Müller P., Bliesath H., Lühmann R., Hartmann M., Huber R., Wurst W.; *Single intravenous administration of the H^+,K^+-ATPase inhibitor BY1023/SK&F96022 - inhibition of pentagastrin-stimulated gastric acid secretion and pharmacokinetics in man;* Aliment. Pharmacol. Therap. 1990a; 4:239-245.

15. Simon B., Müller P., Hartmann M., Bliesath H., Lühmann R., Huber R., Bohnenkamp W., Wurst W.; *Pentagastrin-stimulated gastric acid secretion and pharmacokinetics following single and repeated intravenous administration of the gastric H^+,K^+-ATPase inhibitor Pantoprazole (BY1023/SK&F96022) in healthy volunteers;* Z. Gastroenterol. 1990b; 9:443-447.

16. Simon B., Muller P., Marinis E., Lühmann R., Huber R., Hartmann M., Wurst *W.; Effect of repeated oral administration of BY1023/SK&F96022 - a new substituted benzimidazole derivative - on pentagastrin-stimulated gastric acid secretion and pharmacokinetics in man;* Aliment. Pharmacol. Therap. 1990c; 4:373-379.

17. Steinijans VW, Huber R, Hartmann M, Zech K, Bliesath H, Wurst W, Radtke HW. *Lack of pantoprazole drug interactions in man: an updated review.* Internal J Clin Pharmacol Therap 1996;34:S31-S50.

18. Wurzer H, Schutze K, Bethke T, Fischer R, Lühmann R, Riesenhuber C. *Efficacy and safety of pantoprazole in patients with gastroesophageal reflux disease using an intravenous-oral regimen.* Hepato-Gastroenterology 1999; 46: 1809-1

19. PANTO® IV Product Monograph (Takeda Canada Inc.), Revision date: February 21, 2013, Control No: 161774.

PART III: CONSUMER INFORMATION

[Pr] Dom-PANTOPRAZOLE
pantoprazole sodium for injection

This leaflet is part III of a three-part "Product Monograph" published when Dom-PANTOPRAZOLE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dom-PANTOPRAZOLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Dom-PANTOPRAZOLE is used (short-term, up to 7 days) to treat acid-related stomach problems such as reflux esophagitis (a severe form of heartburn), and pathological hypersecretory conditions (conditions in which the stomach produces large amounts of acid) including Zollinger-Ellison syndrome (ZES). Dom-PANTOPRAZOLE is used mainly in hospitals in patients who cannot take oral medication.

What it does:
Dom-PANTOPRAZOLE works by reducing the amount of acid made in your stomach.

When it should not be used:
You should not take Dom-PANTOPRAZOLE if you think you might be allergic to any of the ingredients (see "What the non-medicinal ingredients are").

What the medicinal ingredient is:
Pantoprazole sodium sesquihydrate.

What the non medicinal ingredients are:
Sodium hydroxide and water.

What dosage forms it comes in:
Powder for injection : 40 mg pantoprazole/vial

Your doctor might switch you to pantoprazole tablets as soon as you can start taking oral medications again.

WARNINGS AND PRECAUTIONS

Your doctor will decide if you should receive Dom-PANTOPRAZOLE. BEFORE you use Dom-PANTOPRAZOLE talk to your doctor or pharmacist:

- about all health problems you have now or have had in the past;
- about all other medications you take, including ones you can get without a prescription;
- if you are taking atazanavir sulphate advise your doctor as this may interact with Dom-PANTOPRAZOLE;
- if you are allergic to pantoprazole;
- if you are pregnant, plan to become pregnant or are breastfeeding. Excretion into human milk has been reported, discuss this with your doctor;
- about any past problems with the amount of zinc in your blood;
- if you suffer unexplained weight loss, recurrent vomiting or vomiting blood, dark stools, fatigue (anemia) or difficulty in swallowing;
- if you have severe and/or persistent diarrhea, because products which reduce stomach acid have been associated with a small increase in infectious diarrhea.
- if you experience any cardiovascular (e.g. heart) or neurological (e.g. brain) symptoms including palpitations (rapid heartbeat),dizziness, seizures, and tetany(muscle condition with symptoms such as twitching, spasms, cramps and convulsions) as these may be signs of hypomagnesaemia (low magnesium levels in the body)

People who take multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist or spine. You should take Dom-PANTOPRAZOLE exactly as prescribed at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take Dom-PANTOPRAZOLE.

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor or pharmacist if you are taking warfarin. Warfarin may interact with Dom-PANTOPRAZOLE.
Dom-PANTOPRAZOLE may interact with atazanavir sulphate and methotrexate.

Laboratory test interactions with Dom-PANTOPRAZOLE:
Talk to your doctor if you are to take a tetrahydrocannabinol (THC / Cannabis) urine screening test, as Dom-PANTOPRAZOLE can provide a false positive result.

PROPER USE OF THIS MEDICATION

Your doctor will decide what an appropriate dosage of Dom-PANTOPRAZOLE is for you.

Usual adult dose:
For reflux esophagitis the recommended dosage is 40 mg once daily.

For hypersecretory conditions including Zollinger-Ellison syndrome (ZES) the recommended dosage is 80 mg every 12 hours.

Overdose:

In case of drug overdose, contact a healthcare professional (e.g. doctor), hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

Missed Dose:

Contact your doctor or pharmacist immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, Dom-PANTOPRAZOLE may cause side effects in some people. When side effects have been reported, they have been generally mild and did not last a long time. Headache, diarrhea, nausea/vomiting, and general abdominal discomfort are the most common side effects; less often inflammation or bruises from the injection, itchiness, and rash can occur. If any of these become troublesome, consult your doctor. If you experience any unusual or unexpected symptoms while using Dom-PANTOPRAZOLE, consult your doctor.

After stopping your medication, your symptoms may get worse and your stomach may increase the acid production.

Treatment in combination with antibiotics:
If you experience symptoms such as severe (watery or bloody) diarrhea, fever, abdominal pain or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this happens, stop taking these drugs and call your healthcare professional immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Stop taking drug and seek immediate emergency medical attention
Rare	Disturbances in vision*	√
Isolated cases	Liver damage (symptoms include yellowing of the skin and eyes)	√
Isolated cases	Severe skin reactions such as Stevens-Johnson-Syndrome, Erythema multiforme, Exfoliative dermatitis, Toxic epidermal necrolysis, Photosensitivity	√
Isolated cases	Muscle wasting	√

*most cases reported are not serious

This is not a complete list of side effects. For any unexpected effects while taking Dom-PANTOPRAZOLE, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15ºC and 30ºC and protect from light.

REPORTING SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect .

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Dominion Pharmacal at, 1-888-550-6060.

This leaflet was prepared by
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