

PPC Pantoprazole for Injection
H⁺, K⁺-ATPase Inhibitor

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Lyophilized powder for injection/40 mg pantoprazole (as pantoprazole sodium)	None <i>For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

Pantoprazole 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 (> 65 years 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** section of the Product Monograph.

Pediatrics:

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

CONTRAINDICATIONS

Pantoprazole for Injection is contraindicated in patients with a history of hypersensitivity to pantoprazole sodium 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.

Pantoprazole, like all PPIs, should not be concurrently administered with atazanavir. See **DRUG INTERACTIONS**.

WARNINGS AND PRECAUTIONS

General

In the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis, anemia, or melena) and when gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with pantoprazole for injection is instituted since treatment with pantoprazole sodium may alleviate symptoms and delay diagnosis.

Further investigation should be considered if symptoms persist despite adequate treatment.

As with any other intravenous product containing edetate tetrasodium (the salt form of EDTA), which is a potent chelator of metal ions including zinc, zinc supplementation should be considered in patients treated with pantoprazole for injection who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously.

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*.

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** section of the Product Monograph.) 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.

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 AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**.

Renal

The daily dose used in renal insufficient patients, as a rule, should not exceed the recommended dosage regimens. See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and 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. Pantoprazole sodium should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus. See **TOXICOLOGY, Reproduction and Teratology** section of the Product Monograph.

Nursing Women:

Limited data is available around pantoprazole use in nursing women. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Animal studies have shown excretion of pantoprazole in breast milk. 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 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 **PHARMACOLOGY** section of the Product Monograph.

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.

In one tolerability study (n = 61) comparing 40 mg pantoprazole sodium i.v. without EDTA to 40 mg pantoprazole sodium i.v. with EDTA in healthy volunteers, the following treatment emergent adverse events were reported most frequently (i.e., ≥ 1% and < 10%) in the EDTA group: abdominal pain, chest pain, face edema, headache, pain, vasodilation, nausea, vomiting, peripheral edema, dizziness, pruritis, rash, increased triglycerides, increased glucose, decreased hematocrit, decreased neutrophils, and creatinine clearance decreased. Increased potassium, decreased potassium, and increased ALT/SGPT were reported in the non-EDTA group only. Constipation was reported at a frequency of ≥ 10%. Increased triglycerides was reported at a frequency of ≥ 10% in the non-EDTA group only. All of the adverse events were mild or moderate and no significant differences were seen between treatment groups. The EDTA formulation was well tolerated and has a similar tolerability profile to the non-EDTA formulation.

Eight subjects experienced increases in serum eosinophils (3 subjects in the non-EDTA group, 5 in the EDTA group) all of whom were noted to have elevated eosinophils before administration of the first dose. Of these 8 subjects, during the course of the study, serum eosinophils decreased in 3 subjects (all in the EDTA group), stayed approximately the same in 2 subjects (1 EDTA, 1 non-EDTA), and increased slightly in 3 subjects (1 EDTA, and 2 non-EDTA).

Postmarket Adverse Drug Reactions

The following events were reported in postmarketing 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; hyponatremia; 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; pancytopenia; 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; diarrhea; 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; hyperlipidemias and lipid increases; weight changes; body temperature increased; edema peripheral; hypersensitivity (including anaphylactic reactions and anaphylactic shock); bilirubin increased; depression (and all aggravations).

Very rare: thrombocytopenia; leukopenia; disorientation (and all aggravations).

DRUG INTERACTIONS

Overview

Pantoprazole undergoes extensive hepatic metabolism via cytochrome P450-mediated oxidation 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). It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore all PPIs, including pantoprazole, should not be co-administered with atazanavir. See **CONTRAINDICATIONS**.

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, 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 postmarketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

Drug-Food Interactions

Consumption of food does not affect the pharmacokinetics (AUC and C_{max}) of pantoprazole sodium. See **DETAILED PHARMACOLOGY, Human Pharmacology** section of the Product Monograph.

Drug-Laboratory Interactions

There have been reports of false-positive 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 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 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 Pantoprazole 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.

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, USP. 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 Pantoprazole for Injection 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:

Pantoprazole for Injection 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 Pantoprazole for Injection 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 Available Volume (mL)	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 Pantoprazole for Injection 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 of 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.

Treatment of overdosage should be supportive and symptomatic. Pantoprazole is not removed by hemodialysis.

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

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-Elison 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 15 and 30°C. The drug product is sensitive to light. The vials should neither be removed from the provided immediate cardboard carton nor stored outside the carton until ready for use.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pantoprazole for Injection (pantoprazole sodium) is available as 10 mL vials containing 40 mg pantoprazole (42.3 mg pantoprazole sodium) as a lyophilized powder. Available in packages of 1 vial.

Non-medicinal ingredients: edetate tetrasodium, mannitol, and tromethamine.

PHARMACEUTICAL PARTNERS OF CANADA INC.

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