

Pantoprazole for injection BP

PANTOPRAZOLE™ 40 mg

Each Vial contains:
Pantoprazole Sodium IP
eq. to Pantoprazole 40 mg

DESCRIPTION

Pantoprazole is a proton pump inhibitor used to treat erosive esophagitis, gastric acid hypersecretion, and to promote healing of tissue damage caused by gastric acid. The chemical name is Sodium 5-(difluoromethoxy)-2-[[[3,4-dimethoxy-pyridin-2-yl)methyl]sulphonyl]-benzimidazol-1-ide,sesquihydrate. The molecular formula is $C_{16}H_{15}F_2N_3O_5S \cdot 1\frac{1}{2}H_2O$ and its molecular weight is 432.4 g/mol.

THERAPEUTIC INDICATIONS

- Reflux oesophagitis
- Gastric and duodenal ulcer
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

This medicine should be administered by a healthcare professional and under appropriate medical supervision. Intravenous administration of Pantoprazole is recommended only if oral administration is not appropriate. Data are available on intravenous use for up to 7 days. Therefore, as soon as oral therapy is possible, treatment with Pantoprazole I.V. should be discontinued and 40 mg pantoprazole oral should be administered instead.

Gastric and duodenal ulcer, reflux oesophagitis: The recommended intravenous dose is one vial of Pantoprazole (40 mg pantoprazole) per day.

Zollinger-Elison-Syndrome and other pathological hypersecretory conditions

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg Pantoprazole. Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. In case a rapid acid control is required, a starting dose of 2 x 80 mg Pantoprazole is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.

Special populations

Paediatric population: The safety and efficacy of Pantoprazole in children aged under 18 years have not been established. Therefore, Pantoprazole is not recommended for use in patients below 18 years of age.

Hepatic Impairment: A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (See Special warning and precaution for use).

Renal Impairment: No dose adjustment is necessary in patients with impaired renal function (See Pharmacokinetic properties).

Elderly: No dose adjustment is necessary in elderly patients (See Pharmacokinetic properties).

Method of Administration

This medicine should be administered by a healthcare professional and under appropriate medical supervision.

A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection. The prepared solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9 %) solution for injection or glucose 55 mg/ml (5 %) solution for injection.

After preparation the solution must be used within 12 hours. The medicinal product should be administered intravenously over 2-15 minutes.

Don't use if any particle, leakage or breakage is found.

CONTRAINDICATIONS

Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS

Gastric malignancy: Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. 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 or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Hepatic Impairment: In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise of the liver enzymes, the treatment should be discontinued (See Posology and method of administration).

Co-administration with atazanavir: Co-administration of atazanavir with proton pump inhibitors is not recommended. 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.

Gastrointestinal infections caused by bacteria: Gastrointestinal infections caused by bacteria. Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter or C. difficile.

Hypomagnesaemia: Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLÉ): Proton pump inhibitors are associated with very infrequent cases of SCLÉ. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping pantoprazole. SCLÉ after previous treatment with a proton pump inhibitor may increase the risk of SCLÉ with other proton pump inhibitors.

Bone fractures: Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Interference with laboratory tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, pantoprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

DRUG INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

Medicinal products with pH Dependent Absorption Pharmacokinetics: Because of profound and long-lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV protease inhibitors: 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.

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin): Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

Methotrexate: Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients.

Therefore, in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interactions studies: Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4. Interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, gliclazamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions. An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin. There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19: Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment. Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John's wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

PREGNANCY, LACTATION AND FERTILITY

Pregnancy: A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of pantoprazole. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation: Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion into human milk but excretion into human milk has been reported. A risk to the new born/infant cannot be excluded. Therefore, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Pantoprazole should be made considering the benefit of breast-feeding to the child and the benefit of Pantoprazole therapy to woman.

Fertility: There was no evidence of impaired fertility following the administration of pantoprazole in animal studies.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole has no or negligible influence on the ability to drive and use machines.

Adverse drug reactions such as dizziness and visual disturbances may occur (See undesirable effects). If affected, patients should not drive or operate machines.

UNDESIRABLE EFFECTS

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a "not known" frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Agranulocytosis	Thrombo-cytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid (triglycerides, cholesterol); Weight changes		Hyponatraemia; Hypomagnesaemia; Hypocalcaemia(1); Hypokalaemia(1)
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)

Nervous system disorders		Headache, Dizziness	Taste disorders		Paresthesia
Eye disorders			Disturbances in vision/ blurred vision		
Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea; Nausea/ vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			Microscopic colitis
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ -GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus, Drug reaction with eosinophilia and systemic symptoms DRESS
Musculo-skeletal and connective tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		Muscle spasm ⁽²⁾
Renal and urinary disorders					Tubointerstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

OVERDOSE

There are no known symptoms of overdose in man. Systemic exposure with up to 240 mg administered intravenously over 2 minutes was well tolerated. Pantoprazole is extensively protein bound, it is not readily dialyzable. In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Drugs for acid related disorders, Proton pump inhibitors

ATC Code: A02BC02

Mechanism of action: Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H^+ , K^+ -ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

Pharmacodynamic effects

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments have not been observed in humans.

An influence of a long-term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies. During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Pharmacokinetic properties

General Pharmacokinetics: Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Distribution: Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

Biotransformation: The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, another metabolic pathway include oxidation by CYP3A4.

Elimination: Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

Special populations

Poor metabolisers: Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Renal impairment: No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2 - 3 h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment: Although for patients with liver cirrhosis (classes A and B according to Child) the half-life time values increased to between 7 and 9 h and the AUC values increased by a factor of 5-7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

Elderly people: A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

Pediatric population: Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 - 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

STORAGE: Store below 25°C, Protect from light.

Don't use Pantoprazole injection after the expiry date printed on label and carton.

Keep Out of reach of Children.

PRESENTATION:

Primary Packing: 10 ml clear glass vial USP Type-I.

Secondary Packing: Each vial and 10 ml WFI are packed in printed mono carton along with package insert.

Mfd. by:

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