

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PANTOCID 40MG IV INJECTION

2. QUALITATIVE AND QUANTITATIVE

COMPOSITION PANTOCID IV INJECTION

Each vial contains:

Pantoprazole 40 mg

Excipients: For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Intravenous administration of pantoprazole injection is recommended only if oral administration is not appropriate. Intravenous use for up to 7 days has been reported. Therefore, as soon as oral therapy is possible, treatment with pantoprazole injection i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Posology

Gastric and duodenal ulcer, reflux oesophagitis

The recommended intravenous dose is one vial of pantoprazole (40 mg pantoprazole) per day.

Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hyper secretory 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.

Patients with 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 section 4.4).

Patients with renal impairment

No dose adjustment is necessary in patients with impaired renal function (see section 5.2).

Older people

No dose adjustment is necessary in older patients (see section 5.2).

Paediatric population

The safety and efficacy of pantoprazole 40 mg powder for solution for injection in children aged under 18 years have not been reported. Therefore, pantoprazole 40 mg powder for solution for injection is not recommended for use in patients below 18 years of age.

Method of administration

A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection. For instructions for preparation see section 6.6. 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.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

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 section 4.2).

Co-administration with HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Gastrointestinal infections caused by bacteria

Treatment with pantoprazole may lead to a slightly increased risk of

gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially 'sodium-free'.

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 has been reported to be improved after magnesium replacement and discontinuation of the PPI.

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

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 older people or in the presence of other recognised risk factors. Proton pump inhibitors have been reported to 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.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors have been reported to be associated with very infrequent cases of SCLE. 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 healthcare professional should consider stopping pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH Dependent Absorption Pharmacokinetics

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV protease inhibitors

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability (see section 4.4).

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)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

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 metabolized 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.

No clinically significant interactions has been reported with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol.

An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.

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.

No interactions with concomitantly administered antacids have been reported.

No clinically relevant interactions have been reported by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of reported data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of pantoprazole.

Reported animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of pantoprazole during pregnancy.

Breast-feeding

Pantoprazole has been reported to be excreted in breast milk. There is insufficient reported information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/abstain from pantoprazole therapy should take into account the benefit of breast-feeding for the child, and the benefit of pantoprazole therapy for the woman.

Fertility

No evidence of impaired fertility following the administration of pantoprazole has been reported (see section 5.3).

4.7 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 section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADR is injection site thrombophlebitis. Diarrhoea and headache has been reported in approximately 1 % of patients.

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

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

Adverse reactions reported with pantoprazole have been tabulated below:

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders	—	—	Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	—
Immune system disorders	—	—	Hypersensitivity (including anaphylactic reactions and anaphylactic shock)	—	—

Metabolism and nutrition disorders	—	—	Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes	—	Hyponatraemia; Hypomagnesaemia (see section 4.4); Hypocalcaemia in association with hypomagnesaemia (1); Hypokalaemia
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	—	Paraesthesia	—
Eye disorders	—	Disturbances in vision / blurred vision	—	—	—

Gastrointestinal disorders	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 subcutaneous tissue disorders	—	Rash/exanthema/eruption; Pruritus	Urticaria; Angioedema	—	Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	—	Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia	—	Muscle spasm (2)
Renal and urinary disorders	—	—	—	—	Interstitial nephritis (with possible progression to renal failure)

Reproductive system and breast disorders	—	—	Gynaecomastia	—	—
General disorders and administration site conditions	—	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral	—	—

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

There are no known symptoms of overdose in man.

Systemic exposure with up to 240 mg administered intravenously over 2 minutes, have been reported to be well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 blockade of

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 have been reported to 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, has been reported only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach has been reported in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids reported in animal (see section 5.3) have not been reported 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.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion have been reported. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

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.

5.2 Pharmacokinetic properties

General pharmacokinetics

Pharmacokinetics does not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole have been reported to be 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, other metabolic pathway includes oxidation by CYP3A4.

Elimination

Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. A few cases of subjects with delayed elimination have been reported. 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 is 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 have been reported to be approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations have been reported to be 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 (incl. 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 values have been reported to increase to between 7 and 9 h and the AUC values increased by a factor of 5 - 7, the maximum serum concentration have been reported to be only increased slightly by a factor of 1.5 compared with healthy subjects.

Older people

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

Paediatric population

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

5.3 Preclinical safety data

No special hazard to humans has been reported based on conventional reported data of safety pharmacology, repeated dose toxicity and genotoxicity.

In the reported two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas have been reported to be found in the fore stomach of

rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the reported two-year rodent studies an increased number of liver tumors was reported in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid have been reported in the rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In a reported peri-postnatal rat reproduction study designed to assess bone development, signs of offspring toxicity (mortality, lower mean body weight, lower mean body weight gain and reduced bone growth) were reported at exposures (C_{max}) approximately 2x the human clinical exposure. By the end of the recovery phase, bone parameters were similar across groups and body weights were also trending toward reversibility after a drug-free recovery period. The increased mortality has only been reported in pre-weaning rat pups (up to 21 days age) which is estimated to correspond to infants up to the age of 2 years old. The relevance of this finding to the paediatric population is unclear. A previous reported peri-postnatal study in rats at slightly lower doses found no adverse effects at 3 mg/kg compared with a low dose of 5 mg/kg in this study.

No evidence of impaired fertility or teratogenic effects has been reported.

Penetration of the placenta have been reported to increase with advanced gestation in rat. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

None

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C.

6.4 Special precautions for storage

Store up to 25°C, Protected from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Lyophilized cake in 10ml colourless tubular glass vial with grey rubber stopper and blood red flip off aluminium seal.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Ind
Ltd, Sun House, 201 B/1,
Western Express Highway, Goregaon (E), Mumbai - 400063, India

8. MARKETING AUTHORISATION NUMBER

H2005/323/14582/R1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2026 March 15

10. DATE OF REVISION OF THE TEXT

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