Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel

TOPRAZ

Pantoprazole 40 mg Powder for Solution for Injection

1. NAME OF DRUG PRODUCT: Pantoprazole 40 mg Powder for Solution for Injection

(TRADE) NAME OF THE PRODUCT: TOPRAZ

STRENGTH: 40 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Pantoprazole 40 mg Powder for Solution for Injection:
Each vial contains:
Pantoprazole Sodium Sesquihydrate Ph. Eur. equivalent to 40 mg of Pantoprazole.

3. PHARMACEUTICAL FORM
Powder for solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term use for symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux esophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration
The intravenous administration of TOPRAZ is recommended only if oral application is not appropriate. The recommended dose for gastric and duodenal ulcer and moderate and severe reflux esophagitis is one vial of 40mg TOPRAZ per day. For the long-term management of Zollinger-Ellison-Syndrome and other pathological hyper secretory conditions the recommended daily dose at the beginning of the treatment is 80mg TOPRAZ. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage 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 TOPRAZ is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients. Transition from TOPRAZ to the oral formulation of pantoprazole should be performed as soon as it is clinically justified. The recommended intravenous dosage is one vial (40 mg pantoprazole) TOPRAZ per day.

Special Patient Populations Impaired Hepatic function
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole I.V.) should not be exceeded in patients with severe liver impairment

Impaired renal function
No dose adjustment is necessary in patients with impaired renal function.

Type and duration of treatment
As soon as oral therapy is possible, treatment with TOPRAZ should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Method of administration
A ready-to-use solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the powder. This 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.

Glass or plastic containers should be used for dilution.

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

From a microbiological point of view, the product should be used immediately. TOPRAZ should not be prepared or mixed with solvents other than those stated. The medicine should be administered intravenously over 2-15 minutes.

The contents of the vial are for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

4.3 Contraindications
Hypersensitivity to the active substance, substituted benzimidazoles.

4.4 Special warnings and precautions for use
Regular Surveillance
Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

Subacute Cutaneous Lupus Erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (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 health care professional should consider stopping TOPRAZ. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPI like TOPRAZ 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 PPI 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.

Fracture
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.

Clostridium Difficile Diarrhea
Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, TOPRAZ treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). 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.

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, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate
Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Gastric malignancy
Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.

Hepatic Impairment
In patients with severe liver impairment the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of pantoprazole on the absorption of other medicinal products
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 such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV medications (atazanavir)
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.

Coumarin anticoagulants (phenprocoumon or warfarin)
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 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.

Drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol, did not reveal clinically significant interactions.

Results 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.

No clinically relevant interactions were found by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin).

4.6 Pregnancy and lactation
Pregnancy
There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. TOPRAZ should not be used during pregnancy, unless clearly necessary.

Breast-feeding
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore, a decision on whether to discontinue breast-feeding or to discontinue/ abstain from TOPRAZ therapy should take into account the benefit of breastfeeding for the child, and the benefit of TOPRAZ therapy for the woman.

4.7 Effects on ability to drive and use machines
Adverse drug reactions, such as dizziness and visual disturbances may occur (see section Undesirable effects). If affected, patients should not drive or operate machines.

4.8 Undesirable effects
The most commonly reported (Adverse Drug Reachtion) ADR is injection site thrombophlebitis. The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Very common; common; uncommon; rare; very rare, not known. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole Experience.

Frequency / **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)		
Infections and infestations					*Clostridium difficile* associated diarrhea.
Nervous System		Headache;	Taste disorders		
disorders		dizziness			
Reproductive system and breast disorders			Gynaecomastia		
Metabolism and nutrition disorders			Hyperlipidae-mias, Weight changes		Hyponatraemia; Hypomagne-saemia; Vitamin B12 deficiency
Psychiatric disorders		Sleep disorders	Depression	Disorientation	Hallucination Confusion

Black A/s: 210 x 360 mm

AUROBINDO Packaging Development	Product Name: TOPRAZ	Component: Leaflet	Item Code: P1542476	Date & Time: 13.05.2026 & 12.00 PM
	Customer / Country: Malaysia-Eugia-Unit III	Version No.: 00	Reason Of Issue: Revision	Reviewed / Approved by
Team Leader: Ariff	Dimensions: 210 x 360 mm	No. of Colours : 01		
Initiator: Vijay				
Artist: MJ Designers (Jaipal)	Pharmacode: 42476			
Additional Information : Supersede item Code: P1542301				Sign / Date

Nervous system disorders		Headache; Dizziness	Taste disorders		Parasthesia
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			
Hepatobiliary disorders		Liver enzymes increased (transaminase s, 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
Musculoskeletal And connective Tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		
Renal and urinary disorders					Interstitial Nephritis
General disorders and administration site conditions	Injection site thrombophlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

5 SYMPTOMS AND TREATMENT OF OVERDOSE

There are no known symptoms of overdose in man.

Systemic exposure with up to 240 mg administered intravenously over 2 minutes, were 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.

6 PHARMACOLOGICAL PROPERTIES

6.1 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.

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).

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid.

Pharmacodynamic effects:
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.

6.2 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 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; other metabolic pathway includes 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 is excreted with the faeces. The main metabolite in both the serum and urine is desmethyl pantoprazole 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 (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 (2-3h), 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 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.

Older people:
A slight increase in AUC and Cmax 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 there was no significant association between Pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Disodium edetate,
Sodium hydroxide,
Water for injection

7.2 Product Description

*Before reconstitution***:** Freeze dried, white to off-white, porous cake or powder in a clear glass vial stoppered with grey slotted rubber stopper and sealed with aluminum seals having Sky Blue color PP disc.

*After reconstitution***:** Clear and colorless to very slightly yellow solution.

7.3 Shelf life

Unopened vial: 24 months.
After reconstitution, or reconstitution and dilution, chemical and physical in use stability has been demonstrated for 12 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

7.4 Special precautions for storage

Do not store above 30°C.

Keep the vial in the outer carton in order to protect from light.

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

7.5 Nature and contents of container

Mono Vial (one vial/carton)

10 mL Type-I, Tubular clear glass vial that are closed using ready to use gray bromobutyl rubber stoppers and sealed with aluminum seals with sky blue colour polypropylene disk. Pantoprazole 40 mg Powder for Solution for Injection packed in the above vials will be further placed in a suitable carton along with a package insert.

MANUFACTURED BY:

EUGIA PHARMA SPECIALITIES LIMITED,
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DATE OF REVISION OF THE TEXT

April 2026.

P1542476