1.5.3 Patient Information Leaflet (PIL) or Package Insert

PANTIN (Pantoprazole Sodium for Injection 40 mg/vial)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

Keep this leaflet. You may need to read it again.

If you have any further questions, please ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. WHAT PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL IS AND WHAT IT IS USED FOR

Gastro esophageal Reflux Disease Associated with a History of Erosive Esophagitis

Pantoprazole Sodium For Injection 40 Mg/Vial is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE).

Safety and efficacy of Pantoprazole Sodium For Injection 40 Mg/Vial as a treatment of patients with GERD and a history of EE for more than 10 days have not been demonstrated.

Pathological Hypersecretion Including Zollinger-Ellison Syndrome

Pantoprazole Sodium For Injection 40 Mg/Vial is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome in adults.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL

Pantoprazole Sodium For Injection 40 Mg/Vial is contraindicated in patients with known hypersensitivity reactions including anaphylaxis to the formulation or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

Proton pump inhibitors (PPIs), including PROTONIX I.V., are contraindicated in patients receiving rilpivirine-containing products.

Table 1 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL and instructions for preventing or managing them.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.

Table 1: Clinically Relevant Interactions Affecting Drugs Co-Administered with Pantoprazole Sodium For Injection 40 Mg/Vial and Interaction with Diagnostics

Antiretrovirals	
Clinical Impact:	The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with pantoprazole may reduce antiviral effect and promote the development of drug resistance. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may

	increase toxicity of the antiretroviral drugs. • There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL is contraindicated. See prescribing information. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information.
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
Clopidogrel	
Clinical Impact:	Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition.

Intervention:	No dose adjustment of clopidogrel is necessary when administered with an approved dose of PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL
Methotrexate	
Clinical Impact:	Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted.
Intervention:	A temporary withdrawal of PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL may be considered in some patients receiving high-dose methotrexate.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	
Clinical Impact:	Pantoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): Co-administration of pantoprazole sodium in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving Pantoprazole Sodium For Injection 40 Mg/Vial and MMF. Use Pantoprazole Sodium For Injection 40 Mg/Vial with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.

Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors.
Intervention:	Temporarily stop Pantoprazole Sodium For Injection 40 Mg/Vial treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.

Teratogenic Effects

Pregnancy Category C

Reproduction studies have been performed in rats at intravenous pantoprazole doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) with administration of pantoprazole sodium during organogenesis in pregnant animals and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day on a body surface area basis) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND 4) through PND 21, the pups were

administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in humans at a dose of 40 mg). There were no drug-related findings in maternal animals. During the preweaning dosing phase (PND 4 to 21) of the pups, there were increased mortality and/or moribundity and decreased body weight and body weight gain at 5 mg/kg/day (approximately equal exposures (AUC) in humans receiving the 40 mg dose) and higher doses. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses. The femur findings included lower total area, bone mineral content and density, periosteal and endosteal circumference, and cross-sectional moment of inertia. There were no microscopic changes in the distal femur, proximal tibia, or stifle joints. Changes in bone parameters were partially reversible following a recovery period, with findings on PND 70 limited to lower femur metaphysis cortical/subcortical bone mineral density in female pups at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses.

There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk of fetal harm. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose of pantoprazole sodium. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole sodium in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use

The safety and effectiveness of Pantoprazole Sodium For Injection 40 Mg/Vial have not been established in pediatric patients.

Animal Toxicity Data

In a pre- and post-natal development toxicity study in rats, the pups were administered oral doses of pantoprazole at 5, 15, and 30 mg/kg/day on postnatal day (PND 4) through PND 21, in addition to lactational exposure through milk. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day and higher doses. Changes in bone parameters were partially reversible following a recovery period.

In neonatal/juvenile animals (rats and dogs) toxicities were similar to those observed in adult animals, including gastric alterations, decreases in red cell mass, increases in lipids, enzyme induction and hepatocellular hypertrophy. An increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, was observed in the fundic mucosa of stomachs in repeated-dose studies. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

Geriatric Use

Of 286 patients in clinical studies of intravenous pantoprazole sodium in patients with GERD and a history of EE, 86 (43%) were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience with oral pantoprazole sodium has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

3. HOW TO TAKE PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL

The recommended adult dosage of Pantoprazole Sodium For Injection 40 Mg/Vial is 40 mg given once daily by intravenous infusion for 7 to 10 days.

Discontinue treatment with PROTONIX® I.V. as soon as the patient is able to receive treatment with PROTONIX Delayed-Release Tablets or Oral Suspension.

Data on the safe and effective dosing for conditions other than those described such as life-threatening upper gastrointestinal bleeds, are not available. Pantoprazole Sodium For Injection 40 Mg/Vial once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions.

Preparation and Administration Instructions for Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

Only for intravenous infusion; other parenteral routes of administration are not recommended.

Fifteen Minute Infusion

1. Reconstitute Pantoprazole Sodium For Injection 40 Mg/Vial with 10 mL of 0.9% Sodium Chloride Injection, USP.

2. Further dilute with 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a final concentration of approximately 0.4 mg/mL.

3. Inspect the diluted Pantoprazole Sodium For Injection 40 Mg/Vial solution visually for particular matter and discoloration prior to and during administration.

4. Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Storage

The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light.

Do not freeze the reconstituted solution.

Two Minute Infusion

1. Reconstitute Pantoprazole Sodium For Injection 40 Mg/Vial with 10 mL of 0.9% Sodium Chloride Injection, USP, to a final concentration of approximately 4 mg/mL.

2. Inspect the diluted Pantoprazole Sodium For Injection 40 Mg/Vial solution visually for particular matter and discoloration prior to and during administration.

3. Administer intravenously over a period of at least 2 minutes.

Storage

The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion and does not need to be protected from light.

Do not freeze the reconstituted solution.

Dosage for Pathological Hypersecretion Including Zollinger-Ellison Syndrome

The recommended adult dosage of Pantoprazole Sodium For Injection 40 Mg/Vial is 80 mg intravenously every 12 hours. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80 mg intravenously every 8 hours is expected to maintain acid output below 10 mEq/h. Daily doses higher than 240 mg or administered for more than 6 days have not been studied. Transition from oral to intravenous and from intravenous to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion. Patients with ZE Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

Preparation and Administration Instructions for Pathological Hypersecretion Including Zollinger-Ellison Syndrome

Only for intravenous infusion; other parenteral routes of administration are not recommended.

Fifteen Minute Infusion

1. Reconstitute each vial of Pantoprazole Sodium For Injection 40 Mg/Vial with 10 mL of 0.9% Sodium Chloride Injection, USP.

2. Combine the contents of the two vials and further dilute with 80 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL.

3. Inspect the diluted Pantoprazole Sodium For Injection 40 Mg/Vial solution visually for particular matter and discoloration prior to and during administration.

4. Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Storage

The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light.

Do not freeze the reconstituted solution.

Two Minute Infusion

1. Reconstitute Pantoprazole Sodium For Injection 40 Mg/Vial with 10 mL of 0.9% Sodium Chloride Injection, USP, per vial to a final concentration of approximately 4 mg/mL.

2. Inspect the diluted Pantoprazole Sodium For Injection 40 Mg/Vial solution visually for particular matter and discoloration prior to and during administration.

3. Administer the total volume from both vials intravenously over a period of at least 2 minutes.

Storage

The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion and does not need to be protected from light.

Do not freeze the reconstituted solution.

Compatibility Information

- Administer Pantoprazole Sodium For Injection 40 Mg/Vial intravenously through a dedicated line or through a Y-site.
- Flush the intravenous line before and after administration of Pantoprazole Sodium For Injection 40 Mg/Vial with either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP.
- When administered through a Y-site, Pantoprazole Sodium For Injection 40 Mg/Vial is compatible with the following solutions: 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP.
- Midazolam HCl has been shown to be incompatible with Y-site administration of PROTONIX I.V.
- Pantoprazole Sodium For Injection 40 Mg/Vial may not be compatible with products containing zinc.
- When Pantoprazole Sodium For Injection 40 Mg/Vial is administered through a Y-site, immediately stop use if precipitation or discoloration occurs.

4. POSSIBLE SIDE EFFECTS

The following serious adverse reactions are described below and elsewhere in labeling:

- Hypersensitivity and Severe Skin Reactions
- Injection Site Reactions
- Potential for Exacerbation of Zinc Deficiency
- Acute Interstitial Nephritis
- Clostridium difficile-Associated Diarrhea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Hepatic Effects
- Hypomagnesemia
- Fundic Gland Polyps

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Worldwide, approximately 80,500 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment.

Gastroesophageal Reflux Disease (GERD)

Safety in nine randomized comparative US clinical trials in patients with GERD included 1,473 patients on oral PROTONIX (20 mg or 40 mg), 299 patients on an H2-receptor antagonist, 46 patients on another PPI, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table 1.

The number of patients treated in comparative studies with Pantoprazole Sodium For Injection 40 Mg/Vial is limited; however, the adverse reactions seen were similar to those seen in the oral studies. Thrombophlebitis was the only new adverse reaction identified with PROTONIX I.V.

Table 1: Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of >2%

	Oral PROTONIX (n= 1473) %	Comparators (n=345) %	Placebo (n=82) %
Headache	12.2	12.8	8.5
Diarrhea	8.8	9.6	4.9
Nausea	7.0	5.2	9.8
Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3.0	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for oral PROTONIX in US clinical trials with a frequency of ≤2% are listed below by body system:

Body as a Whole: allergic reaction, fever, photosensitivity reaction, facial edema, thrombophlebitis (I.V. only)

Gastrointestinal: constipation, dry mouth, hepatitis

Hematologic: leukopenia (reported in ex-US clinical trials only), thrombocytopenia

Metabolic/Nutritional: elevated CPK (creatine phosphokinase), generalized edema, elevated triglycerides, liver function tests abnormal

Musculoskeletal: myalgia

Nervous: depression, vertigo

Skin and Appendages: urticaria, rash, pruritus

Special Senses: blurred vision

Zollinger-Ellison (ZE) Syndrome

In clinical studies of ZE Syndrome, adverse reactions reported in 35 patients administered Pantoprazole Sodium For Injection 40 Mg/Vial doses of 80 mg to 240 mg per day for up to 2 years were similar to those reported in adult patients with GERD.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROTONIX and Pantoprazole Sodium For Injection 40 Mg/Vial. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are listed below by body system:

General Disorders and Administration Conditions: asthenia, fatigue, malaise
Immune System Disorders: anaphylaxis (including anaphylactic shock), systemic lupus erythematosus
Investigations: weight changes
Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), angioedema (Quincke's edema) and cutaneous lupus erythematosus
Musculoskeletal Disorders: rhabdomyolysis, bone fracture
Renal and Urinary Disorders: interstitial nephritis
Hepatobiliary Disorders: hepatocellular damage leading to jaundice and hepatic failure
Psychiatric Disorder: hallucinations, confusion, insomnia, somnolence
Metabolism and Nutritional Disorders: hyponatremia, hypomagnesemia
Infections and Infestations: Clostridium difficile-associated diarrhea
Hematologic: pancytopenia, agranulocytosis
Nervous: ageusia, dysgeusia
Gastrointestinal Disorders: fundic gland polyps

5. HOW TO STORE PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL

Store below 30°C, Protect from light.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL

The active substance is Pantoprazole sodium.

Each vial contains Pantoprazole Sodium USP equivalent to Pantoprazole 40mg.

The other ingredients are: Edetate Disodium USP, Sodium Hydroxide USP-NF, Water for Injection IH

What PANTOPRAZOLE SODIUM FOR INJECTION 40 MG/VIAL looks like and contents of the pack

White to off white Lyophilized cake or powder in Type-I 10 ml Tubular vials sealed with 20 mm grey bromobutyl rubber stopper and White color flip off aluminum seal.

When constituted as directed the solution should be colorless to light yellow color, clear solution Pantoprazole Sodium for Injection 40 mg/vial are available in:

Blister pack: 1×1's Pack: 10 mL Clear Tubular Glass Vial

Marketing Authorization Holder and Manufacturer

Marketing Authorisation Holder:

Name: **Hetero Labs Limited**

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Manufacturer:

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