Front

zotonix®
(Pantoprazole)
40 mg

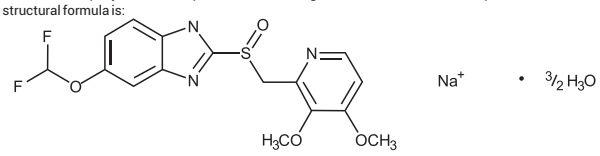
IV
Injection

ذوٹونِکس انجکشن

COMPOSITION:
Each vial contains:
Pantoprazole (as Sodium) ..... 40 mg.
Lyophilized Powder

Product Specs.: BP

DESCRIPTION:
The active ingredient in Pantoprazole Sodium for Injection, a PPI, is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO4S \cdot 1.5\ H2O$, with a molecular weight of 432.37. The structural formula is:



Clinical Pharmacology:
Mechanism of Action: Pantoprazole is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).
Pharmacodynamics:
Antisecretory Activity: The magnitude and time course for inhibition of pentagastrin-stimulated acid output (PSAO) by single intravenous doses (20 to 120 mg) of pantoprazole were assessed in a single-dose, open-label, placebocontrolled, dose-response study. The results of this study are shown in Table 2. Healthy subjects received a continuous infusion for 25 hours of pentagastrin (PG) at 1 mcg/kg/hour, a dose known to produce submaximal gastric acid secretion. The placebo group showed a sustained, continuous acid output for 25 hours, validating the reliability of the testing model. Intravenous administration of pantoprazole sodium had an onset of antisecretory activity within 15 to 30 minutes of administration. Intravenous doses of 20 to 80 mg of pantoprazole substantially reduced the 24-hour cumulative PSAO in a dose-dependent manner, despite a short plasma elimination half-life. Complete suppression of PSAO was achieved with 80 mg within approximately 2 hours and no further significant suppression was seen with 120 mg. The duration of action of intravenous pantoprazole sodium was 24 hours.In one study of gastric pH in healthy subjects, pantoprazole was administered orally (40 mg enteric coated tablets) or intravenously (40 mg) once daily for 5 days and pH was measured for 24 hours following the fifth dose. The outcome measure was median percent of time that pH was ⩾4 and the results were similar for intravenous and oral medications; however, the clinical significance of this parameter is unknown.
Serum gastrin effects: Serum gastrin concentrations were assessed in two placebo-controlled studies. In a 5-day study of oral pantoprazole with 40 and 60 mg doses in healthy subjects, following the last dose on day 5, median 24-hour serum gastrin concentrations were elevated by 3 to 4-fold compared to placebo in both 40 and 60 mg dose groups. However, by 24 hours following the last dose, median serum gastrin concentrations for both groups returned to normal levels. In another placebo-controlled, 7-day study of 40 mg intravenous or oral pantoprazole in patients with GERD and a history of EE, the mean serum gastrin concentration increased approximately 50% from baseline and as compared with placebo, but remained within the normal range. During 6 days of repeated administration of intravenous pantoprazole sodium in patients with ZE syndrome, consistent changes of serum gastrin concentrations from baseline were not observed.
Enterochromaffin-Like (ECL) Cell Effects: There are no data available on the effects of intravenous pantoprazole sodium on ECL cells. In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to oral pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by PPIs. However, there were no observed elevations in serum gastrin following the administration of oral pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with oral pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery.
Endocrine effects: In a clinical pharmacology study, pantoprazole 40 mg given orally once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.
Pharmacokinetics: Pantoprazole peak serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses of pantoprazole from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following the administration of intravenous pantoprazole sodium, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In CYP2C19 extensive metabolizers with normal liver function receiving a 40 mg intravenous dose of pantoprazole by constant rate over 15 minutes, the peak concentration (C_{max}) is 5.52±1.42 mcg/mL and the total area under the plasma concentration versus time curve (AUC) is 5.4 ±1.5 mcg hr/mL. The total clearance is 7.6 to 14 L/h.
Distribution: The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.
Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3% of Caucasians and African-Americans and 17 to 23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5 to 10 hours, they still have minimal accumulation (23% or less) with once daily dosing.
Excretion: After administration of a single intravenous dose of 14C-labeled pantoprazole sodium to healthy, extensive CYP2C19 metabolizers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole. also secreted into the bile.

INDICATIONS AND USAGE:
Gastroesophageal reflux disease associated with a history of erosive esophagitis: Pantoprazole Sodium for Injection 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 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 is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome in adults.

DOSAGE AND ADMINISTRATION:
Dosage for gastroesophageal reflux disease associated with a history of erosive esophagitis: The recommended adult dosage of Pantoprazole Sodium for Injection is 40 mg given once daily by intravenous infusion for 7 to 10 days.Discontinue treatment with Pantoprazole Sodium for Injection as soon as the patient is able to receive treatment with pantoprazole sodium 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 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.
For intravenous infusion only.
Fifteen Minute Infusion:
1. Reconstitute Pantoprazole Sodium for Injection 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 solution visually for particulate 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/minute.
Dosage for Pathological Hypersecretion Including Zollinger-Ellison Syndrome: The recommended adult dosage of Pantoprazole Sodium for Injection 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:
For intravenous infusion only.
Fifteen Minute Infusion:
1. Reconstitute each vial of Pantoprazole Sodium for Injection 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 solution visually for particulate 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/minute.
For Injection: 40 mg pantoprazole white to off-white lyophilized powder in a single-dose vial for reconstitution.

WARNINGS & PRECAUTIONS:

- ***Gastric Malignancy:*** In adults, symptomatic response to therapy with Pantoprazole Sodium for Injection does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing.
- ***Hypersensitivity and Severe Skin Reactions:*** Anaphylaxis has been reported.
- ***Injection Site Reactions:*** Thrombophlebitis is associated with intravenous use.
- ***Acute Interstitial Nephritis:*** Observed in patients taking PPIs
- Clostridium difficile -Associated Diarrhea: PPI therapy may be associated with increased risk.
- ***Bone Fracture:*** Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine.
- ***Cutaneous and Systemic Lupus Erythematosus:*** Mostly cutaneous; new onset or exacerbation of existing disease; discontinue Pantoprazole Sodium for Injection and refer to specialist for evaluation
- ***Hepatic Effects:*** Elevations of transaminases observed
- ***Hypomagnesemia:*** Reported rarely with prolonged treatment with PPIs.

Special Populations:

Renal impairment: In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects.
Hepatic impairment: In patients with mild to severe hepatic impairment (Child-Pugh Class A to C), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects when pantoprazole sodium was administered orally. Although serum half-life values increased to 7 to 9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. Oral pantoprazole doses higher than 40 mg per day have not been studied in hepatically impaired patients.
Pediatrics: The safety and effectiveness of Pantoprazole Sodium for Injection have not been established in pediatric patients.
Geriatrics: After repeated intravenous administration in elderly subjects (65 to 76 years of age), the AUC and elimination half-life values of pantoprazole were similar to those observed in younger subjects.
Male and female patients: After oral administration there was a modest increase in the AUC and C_{max} of pantoprazole in women compared to men. However, weight-normalized clearance values are similar in women and men.
Pregnancy: Available data from published observational studies did not demonstrate an association of major malformations or other adverse pregnancy outcomes with pantoprazole. Advise pregnant women of potential risk to fetos.
Nursing mothers: The limited data from a single case reports the presence of pantoprazole in human breast milk. There were no effects on the breastfed infant. There are no data on pantoprazole effects on milk production.

CONTRAINDICATIONS:

Pantoprazole Sodium for Injection 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 Pantoprazole Sodium for Injection, are contraindicated in patients receiving rilpivirine-containing products.

DRUG INTERACTIONS:

Antiretrovirals: 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 sodium 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 sodium may increase toxicity.
- There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole sodium.

Rilpivirine-containing products: Concomitant use with Pantoprazole Sodium for Injection is.
Atazanavir: See prescribing information for atazanavir for dosing information.
Nelfinavir: Avoid concomitant use with Pantoprazole Sodium for Injection. See prescribing information for nelfinavir.
Saquinavir: See the prescribing information for saquinavir for monitoring of potential saquinavir-related toxicities. Other antiretrovirals: See prescribing information for
warfarin: Increased INR and prothrombin time in patients receiving PPIs, including pantoprazole sodium, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
Monitor INR and prothrombin time and adjust the dose of warfarin, if needed, to maintain the target INR range.
Concomitant use of pantoprazole sodium 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
Methotrexate: Concomitant use of pantoprazole sodium 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.
A temporary withdrawal of Pantoprazole Sodium for Injection may be considered in some patients receiving high-dose methotrexate.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenoloate mofetil, ketoconazole): Pantoprazole sodium can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
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 and MMF. Use Pantoprazole Sodium for Injection with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
False Positive Urine Tests for THC: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including other formulations of pantoprazole sodium.
An alternative confirmatory method should be considered to verify positive results.

ADVERSE REACTIONS:

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

- Hypersensitivity and Severe Skin Reactions
- Injection Site Reactions
- Acute Interstitial Nephritis
- Clostridium difficile-Associated Diarrhea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Hepatic Effects
- Hypomagnesemia

OVERDOSAGE:

Experience in patients taking very high doses of pantoprazole (greater than 240 mg) is limited. Adverse reactions seen in spontaneous reports of overdose generally reflect the known safety profile of pantoprazole. Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive. Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- For IV use only.
- To be sold on the prescription of a registered medical practitioner only.

INJECTION: The reconstituted solution should be administered within 24 hours after preparation.

PRESENTATION:
Zotonix IV Injection 40 mg : Pack of 1 vial.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف وریدی استعمال کیلئے۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔
انجکشن: تیار شدہ محلول کو ۲۴ گھنٹے کے اندر استعمال کریں۔

Manufactured by:
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Islamabad, Pakistan.

FOR FURTHER INFORMATION PLEASE CONTACT:

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