PROTONIX

COMPOSITION:

Protonix 40mg Tablets
Each enteric coated tablet contains:
Pantoprazole (U.S.P) 40mg
(as Sodium Sesquihydrate)
Product conforms to Manufacturer's Specifications.
Protonix 40mg I.V. Injection
Each vial contains:
Pantoprazole sodium equivalent to Pantoprazole (M.S)... 40mg
Product conforms to Manufacturer's Specifications.

DESCRIPTION:

The active ingredients in PROTONIX (Pantoprazole sodium) is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2[[3,4-dimethoxy-2-pyridinyl) methyl) sulfinyl]-1H-benzimidazole sesquihydrate,a compound that inhibits gastric acid secretion. Empirical formula of tablet is C16 H14 F2 N3 NaO4S x 1.5H2O, with a molecular weight of 432.4. Empirical formula of injection is C16 H14 F2 N3 NaO4S, with a molecular weight of 405.4

CLINICAL PHARMACOLOGY:

Mechanism of Action:
Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond with two sites of the (H+,K+)-ATPase results in a duration of antisecretory effect that persist longer than 24 hours.
Antisecretory Activity:
Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent in gastric acid output occurs after a single oral dose of (20-80mg) or a single dose of intravenous (20-120mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.
PHARMACOKINETICS:
Absorption of Tablet:
The absorption of pantoprazole is rapid, with a Cmax of 2.5 g/mL that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bio-availability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of Pantoprazole with food may delay its absorption up to 2 hours of longer, however, the Cmax and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timings of meal.
Absorption of Injection:
Pantoprazole peak serum concentration (Cmax) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10mg to 80mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.

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Following the administration of pantoprazole I.V. for injection, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour.
Distribution:
The apparent volume of distribution of pantoprazole is approximately 11.0-23.6L, 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 pharmacological activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasins and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (<23%) with once daily dosing.
Elimination:
After a single oral or intravenous dose of 14C-labelled pantoprazole to healthy, normal metabolizer volunteers, 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.

INDICATIONS:

Protonix Tablets
PROTONIX Tablets are indicated for:
Short-Term Treatment Of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
Maintenance Of Healing Of Erosive Esophagitis
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Protonix I.V. Injection
PROTONIX I.V. Injection is indicated for treatment of:
Gastroesophageal Reflux Disease Associated With A History Of Erosive Esophagitis
Pathological Hypersecretion Including Zollinger-Ellison Syndrome

DOSAGE AND ADMINISTRATION:

Protonix Tablets:
Short-Term Treatment of Erosive Esophagitis Associated With GERD
Adults: 40 mg once daily for up to 8 weeks. For adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.
Children (5 years and older):
Based upon body weight
≥ 15 kg to < 40 kg: 20 mg once daily for up to 8 weeks.
≥ 40 kg: 40mg
Maintenance of Healing of Erosive Esophagitis
Adults: 40mg once daily. Controlled studies did not extend beyond 12 months.
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Adults: 40mg twice daily. Dosage regimens should be adjusted to individual patient needs and

should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered.
Protonix I.V. Injection:
Protonix I.V. for injection may be administered intravenously through a dedicated line or through a Y-site. The intravenous line should be flushed before and after administration of Protonix I.V. for injection with either 5% dextrose injection, 0.9% sodium chloride injection or lactated ringer's injection. When administered through a Y-site, pantoprazole sodium I.V. for injection is compatible with the following solutions: 5% dextrose injection, 0.9% sodium chloride injection or lactated ringer's injection.
Midazolam HCl has been shown to be incompatible with Y-site administration of pantoprazole sodium I.V. for injection. Pantoprazole sodium I.V. for injection may not be compatible with products containing zinc. When Protonix I.V. for injection is adminstered through a-Y-site, immediately stop use if precipitation or discoloration occurs.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit.
Treatment of Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis
The recommended adult dose is 40mg pantoprazole given once daily by intravenous infusion 7 to 10 days. Safety and efficacy of pantoprazole sodium I.V. for injection as a treatment of patients with GERD and a history of erosive esophagitis for more than 10 days have not been demonstrated.
For I.V. Infusion:
Protonix I.V. for injection should be reconstituted with 10ml of 0.9% sodium chloride and further diluted (admixed) with 100ml of 5% dextrose injection 0.9% sodium chloride injection or lactated ringer's injection to a final concentration of approximately 0.4 mg/ml. 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 to be protected from light.
Protonix I.V. for injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7ml/min.
For IV Injection:
Protonix I.V. for injection should be reconstituted with 10ml of 0.9% sodium chloride injection to a final concentration of approximately 4mg/ml. 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. Protonix I.V. for injection should be administered intravenously over a period of at least 2 minutes.
Caution: No other solvents / drug for I.V. injection should be used simultaneously in same infusion.
Pathological Hypersecretion Associated with Zollinger-Ellison Syndrome
The dosage of Protonix I.V. for injection in patients with pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions varies with individual patients. The recommended adult dosage is 80mg q12h. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80mg q8h 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 I.V. and from I.V. 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 Zollinger-Ellison Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

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For IV infusion:
Each vial of Protonix I.V. for injection should be reconstituted with 10ml of 0.9% sodium injection. The contents of the two vials should be combined and further diluted (admixed) with 80ml of 5% dextrose injection 0.9% sodium chloride injection or lactated ringer's injection to a total volume of 100ml with a final concentration of approximately 0.8mg/ml. 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.
Protonix I.V. for injection should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7ml/min.
For IV injection:
Protonix I.V.for injection should be reconstituted with 10ml of 0.9% sodium chloride injection per vial to a final concentration of approximately 4mg/ml. 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. The total volume from both vials should be administered intravenously over a period of at least 2 minutes.
OR as directed by the physician.
NOTE: The reconstituted and diluted solutions should not be used if it contains visible particulate matter.

DIRECTIONS FOR RECONSTITUTION:

For IV injection
Reconstitute the vial contents by vigorous shaking using 10ml 0.9% w/v sodium chloride injection.
For IV infusion
Reconstitute the vial contents by vigorous shaking using 10ml 0.9% w/v sodium chloride injection and further diluted (admixed) with 100ml of 5% dextrose injection, 0.9% sodium chloride injection or lactated ringer's injection.

CONTRAINDICATIONS:

Known hypersensitivity to any component of the formulation.

PRECAUTIONS:

Tablets:
General
Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy. Owing to the chronic nature to errosive esophagitis, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare type of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.
Information for Patients
PROTONIX enteric coated Tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed. Concomitant administration of antacids does not affect the absorption of pantoprazole.

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Injection:
General
Immediate hypersensitivity reactions: Anaphylaxis has been reported with use of intravenous pantoprazole. This way require emergency medical treatment.
Injection site reaction: Thrombophlebitis was associated with the administration of intravenous pantoprazole. Hepatic effects: Mild, transient transaminase elevations have been observed in clinical studies. The clinical significance of this finding in a large population of subjects administered intravenous pantoprazole is unknown.
Symptomatic response to therapy with pantoprazole dose not preclude the presence of gastric malignancy.

PREGNANCY & LACTATION:

Pregnancy Category B
Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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 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.

DRUG- DRUG INTERACTIONS:

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustments is needed with concomitant use of the following drugs: theophylline, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradoil), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not be necessary. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids. Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bio-availability (e.g. ketoconazole, ampicillin esters, and iron salts).

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ADVERSE DRUG REACTIONS:

Body as a whole: Abdominal pain, headache, injection site reaction (including thrombophlebitis and abscess).
Disgestive system: Constipation, dyspepsia, nausea, diarrhea
Nervous system: Insomnia, dizziness.
Respiratory system: Rhinitis.

OVER DOSAGE:

Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

INSTRUCTIONS:

Store in a cool & dry place below 25OC.
Protect from light, heat and moisture.
Keep out of reach of children.
Improper storage may deteriorate the medicine.
The reconstituted solution should be administered within 24 hours after preparation

PRESENTATION:

Tablets: Protonix 40mg Tablets are available in a blister pack of 30's.
Injection: Protonix 40mg is a lyophilized powder available as one vial per pack with one 0.9% w/v sodium chloride injection.