4 1

180mm

120 mm

Presence of gastric malignancy
Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy. Condition of healed GERD treated for up to 40 months with rabeprazole were reported with serial gastric biopsies. Condition without *H. pylori* infection has no clinically important pathologic changes in the gastric mucosa. Condition with *H. pylori* infection at baseline can have mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Condition with mild grades of infection or inflammation in the gastric body tends to change to moderate, whereas those grades moderate at baseline tends to remain stable. Mild grades of infection or inflammation in the gastric antrum tends to remain stable.
Renal impairment
No dose adjustment is necessary in patients with renal impairment.
Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Administration of rabeprazole in mild to moderate liver impairment results in increased exposure and decreased elimination. Caution should be exercised in patients with severe hepatic impairment.

USE IN SPECIFIC POPULATIONS
Use in Pregnancy
There are 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.
Use in Lactation
Since many drugs are excreted in milk, caution should be exercised when rabeprazole is administered to a nursing mother.
Pediatric use
The safety and effectiveness of rabeprazole in pediatric patients has not been established.
Geriatric use
No overall differences in safety or effectiveness were observed between adults and geriatrics.

ADVERSE REACTIONS
Pain, pharyngitis, flatulence, infection, constipation, headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

OVERDOSAGE
There has been no experience with large overdoses of rabeprazole. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

STORAGE
- Store below 30°C in a dry place
- Protect from light and moisture
- Keep out of reach of children.

SHELF LIFE
24 Months

PRESENTATION
Rabeprazole Sodium for Injection is available in a 5 ml 20 mm Flint Tubular Type I vial containing Rabeprazole Sodium 20mg.

MEGA We care

Manufactured for :
MEGA LIFESCIENCES Public Company Limited
Samutprakarn, Thailand.

Manufactured by :
NAPROD LIFE SCIENCES PVT. LTD.
Plot No. G-17/1, M.I.D.C., Tarapur, Boisar, Thane 401506, Maharashtra state, India.

Item Code Artwork Code

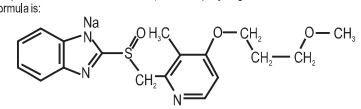
For the use of a Registered Medical Practitioner or a Hospital only

BAROLE INJECTION

Rabeprazole Sodium for Injection 20 mg

COMPOSITION
Each vial contains:
Rabeprazole Sodium.....20mg
Excipients.....q.s.

DESCRIPTION
The active ingredient in Rabeprazole for Injection is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The structural formula is:



INACTIVE INGREDIENTS
Mannitol, Sodium carbonate, Sodium hydroxide and Water for Injection.

AVAILABLE FORM
A white to pale yellow coloured lyophilized mass

CLINICAL PHARMACOLOGY
Mechanism of Action
PHARMACODYNAMICS
Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+/K+ ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

1234

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. Rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.
Antisecretory Activity
The anti-secretory effect begins within one hour after oral administration of 20 mg rabeprazole. The median inhibitory effect of rabeprazole on 24 hour gastric acidity is 88% of maximal after the first dose. Rabeprazole 20 mg inhibits basal and peptone meal-stimulated acid secretion, and increases the pH

Manufactured for :

71.75 mm

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> 3 percent of a 24- hour period. This relatively prolongs pharmacodynamic action compared to the short pharmacokinetic half-life (1–2 hours) which reflects the sustained inactivation of the H+/K+ ATPase.

Effects on Esophageal Acid Exposure

Rabeprazole 20 mg per day decreases 24-hour oesophageal acid exposure in condition of gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure. The effects on gastric acid esophageal pH can be significant and substantial after one day treatment and more pronounced after seven days treatment.

Rabeprazole 20 mg and 40 mg per day, have significant effects on gastric and esophageal pH after one day of treatment, and more pronounced after seven days of treatment.

Effects on Serum Gastrin

Rabeprazole for up to eight weeks to treat ulcerative or erosive esophagitis and for up to 52 weeks to prevent recurrence of disease, increases median fasting gastrin level in a dose related manner. Poor metabolizers can develop significantly higher serum gastrin concentrations than extensive metabolizers.

Effects on Enterochromaffin-like (ECL) Cells

Increased serum gastrin secondary to antisecretory agents can stimulate proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia.

Rabeprazole (10 or 20 mg/day) for up to one year, can develop the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton-pump inhibitor.

Endocrine Effects

There are no clinically reported effects of Rabeprazole on Endocrine system.

Other Effects

No systemic effects and data is reported on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems. No data are available on long-term treatment with rabeprazole and ocular effects.

PHARMACOKINETICS

After oral administration of 20 mg rabeprazole, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours (T_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Absorption and distribution

Absolute bioavailability of Rabeprazole for Injection is 100%. Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism

Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. Rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. The thioether metabolite is formed non-enzymatically by reduction of rabeprazole. Rabeprazole metabolism is slow in poor metabolizers.

Elimination

Following a single 20 mg oral dose of rabeprazole, approximately 90% of the drug is eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose is recovered in the feces. No unchanged rabeprazole is recovered in the urine or feces.

SPECIAL POPULATIONS

Geriatric: After oral administration of rabeprazole 20 mg once daily for seven days, AUC values approximately gets doubled and the C_{max} increases by 60%. There is no reported data evidence of drug accumulation after once daily administration.

Pediatric: The pharmacokinetics of rabeprazole in pediatric patients under the age of 18 years has not been studied.

Gender and Race: No significant differences between male and female subjects with respect to analysis adjusted for body mass and height.

Renal Impairment: No clinically significant differences are reported in the pharmacokinetics of rabeprazole after a single 20 mg oral dose.

Hepatic Impairment: In chronic mild to moderate compensated cirrhosis of the liver administered 20 mg dose of rabeprazole, shows doubled $AUC_{0-\infty}$, 2- to 3- fold higher elimination half-life, and decreased total body clearance up to half compared to values in healthy men. For multiple dose administration in mild to moderate hepatic impairment, the administered 20 mg rabeprazole once daily for eight days, shows increased values approximately by 20% of $AUC_{0-\infty}$ and C_{max}. No information exists on rabeprazole disposition in patients with severe hepatic impairment.

INDICATIONS

Rabeprazole for Injection is an alternative in patients for whom oral administration of rabeprazole is not indicated.

Rabeprazole for Injection is indicated in the treatment of:

1. Sequential-therapy (step-up) from oral rabeprazole, e.g. a patient previously on oral rabeprazole who is temporarily unable to take oral medication for any reason.
2. Active duodenal ulcer with bleeding or severe erosions.
3. Active gastric ulcer with bleeding or severe erosions.
4. Short-term treatment of erosive or ulcerative gastroesophageal reflux disease (GERD)
5. Prevention of acid-aspiration.
6. Stress-induced mucosal injury in critical care.
7. Pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

POSOLOGY AND METHOD OF ADMINISTRATION

The intravenous administration is recommended only in cases where the oral administration is not indicated. As soon as an oral therapy is possible the intravenous therapy should be discontinued.

Recommended dose is intravenous administration of the content of one vial (20 mg rabeprazole) once daily.

Parenteral routes of administration other than intravenous are not recommended.

Injection: The content of the vial needs to be reconstituted with 5 ml sterile water for injection, which should be given slowly over 5-15 min.

Infusion: For intravenous infusion the reconstituted solution should be further diluted and administered as short-term infusion over 15-30 min.

Compatibility with various I.V. fluids

Rabeprazole for Injection is compatible with sterile water for injection and 0.9% sodium chloride injection.

No other solvent or infusion fluid must be used for administration of Rabeprazole for Injection.

Reconstitution

To reconstitute add 5 ml of sterile water for injection to make a solution. After preparation, the reconstituted solution must be used within 4 hours and the unused portion discarded. As with all parenteral admixtures, the reconstituted or further diluted solution should be examined for change in colour, precipitation, haziness or leakage. The unused portion should be discarded.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

WARNINGS & PRECAUTIONS

Bone Fracture

Proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture is increased in patients who received high dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer).

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.

DRUG INTERACTIONS

Drugs metabolized by CPY450

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing).

Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been reported.

Warfarin

There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

Cyclosporine

Rabeprazole inhibits cyclosporine metabolism with an IC 50 of 62 micromolar, in human liver microsomes, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Compounds dependent on gastric pH for absorption

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. Co-administration of rabeprazole and antacids produced no relevant changes in plasma rabeprazole concentrations. Concomitant use of atazanavir and proton pump inhibitors is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Drugs metabolized by CYP2C19

Interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 in extensive metabolizers and poor metabolizers is not reported.

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