RABEPRAZOLE SODIUM

RABELOC 10 **10 mg Enteric-Coated Tablet**
RABELOC 20 **20 mg Enteric-Coated Tablet**
RABELOC I.V. **20 mg Powder for Solution for I.V. injection**

Proton Pump Inhibitor

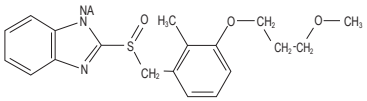
FORMULATION:

RABELOC 10
Each enteric-coated tablet contains:
Rabeprazole Sodium 10 mg

RABELOC 20
Each enteric-coated tablet contains:
Rabeprazole Sodium 20 mg

RABELOC I.V. [Lyophilized]
Each vial contains:
Rabeprazole Sodium 20 mg

DESCRIPTION AND CHEMICAL PROPERTIES:
The active ingredient in Rabeloc I.V is Rabeprazole Sodium for Injection, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole Sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] -methyl]sulfinyl]-1 H benzimidazole sodium salt. It has an empirical formula of C18H20N3NaO3S and a molecular weight of 381.43. The structural formula is shown below:



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 reconstituted solution of **Rabeloc Sodium** with Sterile Water for Injection BP has pH in the range of 8.5to10.5.

Dissolution: Rabeloc Sodium (Rabeloc I.V) gives clear colorless solution on reconstitution with 5 ml Sterile Water for Injection BP. Compatibility with various IV fluids: Rabeloc Sodium (Rabeloc I.V.) is compatible with Dextrose Injection, Dextrose Saline Injection.

PHARMACOLOGICALACTION:

Pharmacodynamics:
Mechanism of Action:
Rabeprazole Sodium belongs to the class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme at the secretory surface of the gastric parietal cell. This enzyme system is regarded as the acid (proton) pump, and therefore Rabeprazole Sodium is classified as a gastric proton-pump inhibitor (PPI) blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.
Anti-secretory Activity:
After oral administration of a 20 mg dose of Rabeprazole Sodium the onset of the anti-secretory effect occurs within one hour with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of Rabeprazole Sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. This duration of pharmacodynamic action is much longer than the pharmacokinetic half-life (approximately one hour) would predict. This effect is probably due to the prolonged binding to the parietal H+/K+-ATPase enzyme. The inhibitory effect of Rabeprazole Sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalizes over 2 to 3 days.

Serum Gastrin Effects:
In clinical studies patients were treated once daily with 10 or 20 mg Rabeprazole Sodium, for up to 24 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pretreatment levels, usually within 1to 2 weeks after discontinuation of therapy.
Pharmacokinetics:
Rabeprazole Sodium is acid-labile, and is therefore administered orally as an enteric-coated (gastro-resistant) tablet formulation. Absorption of Rabeprazole Sodium therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of Rabeprazole Sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of Rabeprazole Sodium and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre systemic metabolism. The absolute bioavailability upon oral administration is robust against food intake or administration of antacids. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. In patients with chronic hepatic disease, the AUC doubled compared to healthy volunteers, reflecting a decreased first pass effect, and the plasma half-life increased 2-3 fold. Rabeprazole Sodium is approximately 97% bound to human plasma proteins. Rabeprazole Sodium undergoes an almost complete, mainly non enzymatic metabolism and forms thioether- Rabeprazole. The main plasma metabolites are thioether (M1) and carboxylic acid (M6). Minor metabolites observed at lower levels include sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5). Only the desmethyl metabolite (M3) has a small amount of antisecretory activity, but it is not present in plasma. Excretion is mainly urinary (90%), with no unchanged drug excreted in the urine. The rest of the metabolites are excreted via the feces. Total recovery was 99.8% implying a low biliary excretion of the metabolites of Rabeprazole Sodium. All PPIs except Rabeprazole Sodium, are metabolized primarily by the hepatic cytochrome P450 enzyme system, and common genetic polymorphisms of the CYP 2C19 isoenzyme affect their clearance and bioavailability. This has been demonstrated to lead to inconsistency in terms of acid suppression across the CYP 2C19 genotypes for all proton pump inhibitors except for Rabeprazole Sodium. Genetic polymorphisms for CYP2C19 do not significantly influence Rabeprazole Sodium clearance, clinical efficacy or potential for drug interactions. In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance <5 ml/min/1.73 m^2), the disposition of Rabeprazole Sodium was very similar to that in healthy volunteers. Elimination of Rabeprazole Sodium was somewhat decreased in the elderly. Following 7 days of daily dosing with 20 mg of Rabeprazole Sodium, the AUC approximately doubled, the Cmax increased by 60% as compared to young healthy volunteers. However there was no evidence of Rabeprazole Sodium accumulation.

INDICATION:
Rabeloc Sodium (Rabeloc I.V.) 20 mg Lyophilized Powder for I.V. Injection is indicated for the treatment of:
1. Sequential-therapy [Step-Up] therapy from oral Rabeloc, e.g. a patient previously on Oral Rabeprazole Sodium who is temporarily unable to take oral Rx for any reason, e.g. during a surgical procedure.
2. Active duodenal ulcer with bleeding or severe erosions
3. Active gastric ulcer with bleeding or severe erosions
4. Severe erosive or ulcerative gastroesophageal reflux disease (GORD/ GERD) or Non-erosive Reflux Disease [NERD] where patient is unable to take oral PPIs.
5. Prevention of Acid-Aspiration during Surgery
6. Stress-induced mucosal injury in critical care, e.g. head-injur burns, MI, etc.

Rabeloc Sodium (Rabeloc 10) 10 mg Enteric-Coated Tablet/ Rabeloc Sodium (Rabeloc 20) 20 mg Enteric-Coated Tablet is indicated for the treatment of:
1. Sequential-therapy [Step-down] therapy from the intravenous Rabeloc Sodium.
2. Active duodenal ulcer
3. Active gastric ulcer
4. Symptomatic erosive or ulcerative gastroesophageal reflux\ disease (GORD/ GERD)or Non-erosive Reflux Disease [NERD].
5. H. Pylori-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics, e.g. Amoxycillin and Clarithromycin.
6. Maintenance treatment of healed erosive or ulcerative GORD.

CONTRAINDICATIONS:
- Patients with known hypersensitivity to Rabeprazole Sodium, substituted benzimidazoles or to any excipient used in the formulation.
- Pregnancy and lactation

DOSAGE AND ADMINISTRATION:
Parenteral routes of administration other than intravenous are not recommended. No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. Doses higher than 40 mg/ day have not been studied in hepatically impaired patients. No dosage adjustment is necessary in patients undergoing hemodialysis. The recommended adult dose, as an

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Size : 120 x 220 mm
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alternative to continued oral therapy, is 20 mg Rabeprazole Sodium given once daily by intravenous bolus over 15 min or by intravenous infusion for 7 to 10 days.

Rabeprazole Sodium must not be given via intramuscular route

Adults/ Elderly:

1. **Active Duodenal Ulcer and Active Benign Gastric Ulcer:** 20 mg to be taken once daily in the morning. Most patients with active duodenal ulcer heal within four weeks. However 2% of patients may require an additional four weeks of therapy to achieve healing. Some patients with active duodenal ulcer may respond to one 10 mg tablet to be taken once daily in the morning. Most patients with active benign gastric ulcer heal within six weeks. However 9% of patients may require an additional six weeks of therapy to achieve healing.
2. **Erosive or Ulcerative Gastro-Esophageal Reflux Disease (GORD):** 20 mg to be taken once daily for four to eight weeks.
3. **Gastro-Esophageal Reflux Disease Long-term Management (GORD Maintenance):** For long-term management up to 12 months, a maintenance dose of Rabeprazole Sodium 10 mg or 20 mg once daily can be used. Some patients may respond to a maintenance dose of 10 mg/day.
4. **Eradication of H. Pylori:** It is indicated for H.Pylori-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics. Rabeprazole Sodium tablets should be taken in the morning, before eating; and although neither the time of day nor food intake was shown to have any effect on Rabeprazole Sodium activity, this regimen will facilitate treatment compliance.
5. **Zollinger Ellison Syndrome:** 60 mg per day range= 20-120 mg per day. Patients should be cautioned that the Rabeprazole Sodium tablets should not be chewed or crushed, but should be swallowed whole.

Special Populations:

The extent of Rabeprazole sodium concentration increase by old age, poor metabolizer status for CYP2C19 and impairment of liver function is not greater than two-fold, impaired renal function does not affect the elimination. Even in patients with delayed elimination, no relevant accumulation of Rabeprazole sodium was observed upon long-term administration. In in-vivo studies, Rabeprazole sodium had no noteworthy effect on the metabolism of other drugs.

Renal and hepatic impairment:

No dosage adjustment is necessary for patients with renal or hepatic impairment. Caution is however advised when Rabeprazole Sodium is first initiated in patients with severe hepatic dysfunction

Children:

It is not recommended for use in children, as there is little experience of its use in this group.

ADVERSE EFFECTS:

The most common adverse events were headache, diarrhea and nausea. Other adverse events were rhinitis, abdominal pain, asthenia, flatulence, pharyngitis, vomiting, non-specific pain/back pain, dizziness, flu syndrome, infection, cough, constipation and insomnia. Further less frequent adverse events were rash, myalgia, chest pain, dry mouth, dyspepsia, nervousness, somnolence, bronchitis, sinusitis, chills, leg cramps, urinary tract infection, arthralgia and fever. In isolated cases, anorexia, gastritis, weight gain, depression, pruritus, vision or taste disturbances, sweating and leukocytosis have been observed. Increased hepatic enzymes have been observed in 2% of patients. There have been reports of thrombocytopenia, neutropenia and leukopenia. Bullous eruptions have been reported and other dermatological reactions including erythema have been reported. Treatment should be stopped immediately at the recurrence of skin lesions.

PRECAUTIONS:

Symptomatic response to therapy with Rabeprazole Sodium does not preclude the presence of gastric or esophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole Sodium. Although no evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls, the prescriber is advised to exercise caution when treatment with Rabeprazole Sodium is first initiated in patients with severe hepatic dysfunction.

INTERACTIONS:

Rabeprazole Sodium undergoes an almost complete, mainly non-enzymatic metabolism with renal elimination of the metabolites. CYP3A4 and CYP2C19 contribute to the fraction of metabolism mediated enzymatically. Studies in healthy subjects have shown that Rabeprazole Sodium does not have clinically significant interactions with other drugs metabolised by the CYP450 system, such as warfarin, phenytoin, theophylline or diazepam. Rabeprazole Sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur therefore the potential for such interaction was investigated. Co administration of Rabeprazole Sodium results in a 33% decrease in ketoconazole levels and a 22% increase in trough digoxin levels in normal subjects. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when such drugs are taken concomitantly with Rabeprazole Sodium. In clinical trials, antacids were used concomitantly with the administration of Rabeprazole Sodium and, in a specific study designed to define this interaction, no interaction with liquid antacids was observed. There was no clinically relevant interaction with food. In vitro studies with human liver microsomes indicated that Rabeprazole Sodium is metabolized by isoenzymes of CYP450 (CYP2C19 and CYP3A4). The studies suggest a low interaction potential; however the effect on cyclosporin metabolism is similar to that observed for other proton pump inhibitors.

OVERDOSAGE:

No specific antidote is known. Rabeprazole Sodium is extensively protein bound and is, therefore, not readily dialysable. Treatment should be supportive and symptomatic.

DIRECTION FOR RECONSTITUTION:

for Rabeprazole Sodium (Rabeloc I.V.):

Each vial is to be reconstituted with 5 mL Sterile Water for Injection.

STORAGE CONDITION:

Rabeprazole Sodium (Rabeloc 10) and (Rabeloc 20) Enteric Coated Tablets:

Store at temperatures not exceeding 30° C. Protect from light & moisture.

Rabeprazole Sodium (Rabeloc I.V.): Store at temperatures not exceeding 30° C. Protect from light. Keep all medicines out of reach of children. After reconstitution with 5 ml of Sterile Water for Injection BP to be used within 4 hours if stored at room temperature and can be used within 24hours if stored in refrigerator. As with all parenteral admixtures, the reconstituted or further diluted solution should be examined for change in color, precipitation, haziness or leakage. The unused portion should be discarded. In case of discoloration of content, please do not use and discard the vial.

AVAILABILITY:

Rabeprazole Sodium (Rabeloc 10) 10 mg Enteric-Coated Tablets:

Strip of ALU-ALU blister 10 tablets (Box of 10 tablets).

Rabeprazole Sodium (Rabeloc 20) 20 mg Enteric-Coated Tablets:

Strip of ALU-ALU blister 10 tablets (Box of 10 tablets).
Strip of ALU-ALU blister 10 tablets (Box of 100's tablets).
Strip of ALU-ALU blister 10 tablets (Box of 50's tablets).

Rabeprazole Sodium (Rabeloc I.V.) 20 mg Powder for Solution for IV injection: 5 ml clear USP Type I glass vial of imported schott tubing with 20mm mouth, 20mm ful slotted grey bromo butyl rubber stopper and 20mm anodized Aluminum flip off blue plain seal.

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse deug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph and Biocare Lifesciences, Inc at (02) 4037032 or e-mail regulatory@biocarelifesciences.com

By reporting undesirable effects, you can help provide more information on the safety of this medicines.

Manufactured by:

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