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

VELOZ INJECTION

RABEPRAZOLE SODIUM INJECTION

(LYOPHILIZED)

Sterile single dose vial

COMPOSITION

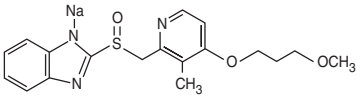
Each Vial contains:

Rabeprazole Sodium I.P. 20 mg

(As Lyophilized Powder)

DESCRIPTION

Rabeprazole Sodium is a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole Sodium is 2-{{[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl} sulphenyl)-1*H*-benzimidazole sodium. It has an empirical formula of $C_{18}H_{20}N_3O_3S.Na$ and a molecular weight of 381.4. Rabeprazole Sodium is a white to light yellow, crystalline powder, hygroscopic. Rabeprazole Sodium is soluble in water. 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 reconstituted solution of Veloz injection with 5 ml of Sterile Water for Injection I.P. has pH in the range of 10 to 12.



Appearance

Rabeprazole Sodium injection gives clear colorless solution on reconstitution with 5ml Sterile Water for Injection I.P.

Compatibility with various IV fluids

Veloz injection is compatible with 0.9% Sodium Chloride Injection I.P., 5% Dextrose injection I.P. and compound sodium lactate injection I.P. (Ringer Lactate solution for Injection). No other solution should be used along with Veloz injection for infusion.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-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.

In gastric parietal cells, Rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied *in vitro*, 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.

PHARMACOKINETICS

Absorption

Absolute bioavailability Rabeprazole I.V. is 100 % .

Distribution

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. *In vitro* studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole). The thioether metabolite is formed non-enzymatically by reduction of Rabeprazole.

Excretion

Following a single 20 mg oral dose of ^{14}C-labeled Rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged Rabeprazole was recovered in the urine or feces.

INDICATIONS AND USAGE

Veloz injection is indicated for the short-term treatment of gastric & duodenal ulcer Gastro-esophageal Reflux Disease (GERD) as an alternative to oral therapy in patients who are unable to take oral proton pump inhibitors

CONTRAINDICATIONS

Patients with known hypersensitivity to Rabeprazole Sodium, substituted benzimidazoles or to any excipient used in the formulation.

DOSAGE AND ADMINISTRATION

Parenteral routes of administration other than intravenous are not recommended.

No dosages adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. The recommended adult dose, as an alternative to continue oral therapy, is 20 mg rabeprazole given once daily by intravenous bolus injection or by intravenous infusion for 7 to 10 days.

Veloz injection should be reconstituted with 5 ml of Sterile Water for Injection IP (provided with this pack) and administered as IV Bolus slowly over a period of 15 minutes.

For Intravenous infusion, Veloz injection should be reconstituted with 5ml of Sterile Water for Injection I.P. and further diluted with 100 ml of 0.9% Sodium Chloride Injection I.P. or 5% Dextrose Injection I.P. or compound sodium lactate injection I.P. to a final concentration of approximately 0.2 mg/ ml. The intravenous line should always be flushed with either 0.9% sodium chloride injection I.P., compound sodium lactate injection I.P. or 5% Dextrose Injection I.P. both prior to and after administration of Veloz injection. After reconstitution, the intravenous infusion solution should be administered as soon as possible over a period of 10 to 30 minutes. (From the in-house compatibility study, it was found that the reconstituted solution is stable (in 100 ml) for up to 2 hours in 0.9% sodium chloride Injection I.P. and 1 hour for 5% Dextrose Injection I.P. and compound sodium lactate injection I.P. in room temperature. The pH of the reconstituted infusion solution is in the range of 9.0 to 10.5 approximately).

INSTRUCTIONS FOR USE

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used.

DIRECTIONS

To be reconstituted with Sterile Water for Injection I.P. (5 ml) provided with this pack.

Reconstituted injection is to be used within 24 hours, if stored below 25^oC.

PRECAUTIONS

General

Symptomatic response to therapy with Rabeprazole does not preclude the presence of gastric malignancy. Safety and efficacy of Rabeprazole sodium in pregnant women, lactating mothers and pediatric population has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In 88/104-week carcinogenicity study in CD-1 mice, Rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to Rabeprazole (AUC) of 1.40 µg•hr/mL, which is 1.6 times the human exposure (plasma AUC_{0-} = 0.88 µg•hr/mL) at the recommended dose for GERD (20 mg/day). Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg•hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic studies were performed in rats at intravenous doses up to 50 mg/kg/day, and in rabbits at intravenous doses up to 30 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to Rabeprazole. There are however no adequate studies in pregnant women. This drug should be used during pregnancy only if clearly needed

Nursing Mothers:

Animal studies have revealed that Rabeprazole is excreted in the milk and it is not well understood whether unmetabolised Rabeprazole is excreted in the milk. Since many drugs are excreted in the milk and because of the potential for adverse reactions to nursing infants from Rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

The cytochrome P450 (CYP450) drug metabolizing enzyme system metabolizes Rabeprazole. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin, theophylline, diazepam (IV), and phenytoin (IV).

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. For example, in normal subjects, co-administration of Rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and Cmax for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with Rabeprazole. Co-administration of Rabeprazole and antacids produced no clinically relevant changes in plasma Rabeprazole concentrations.

Rabeprazole sodium is metabolized by isoenzyme of CYP 450, CYP 2C19 and CYP3A4. The studies the effect on cyclosporin metabolism is similar to that observed for other proton pump inhibitors.

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.

ADVERSE REACTIONS

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, eruction, leg cramps, urinary tract infection, arthralgia and fever.

In isolated cases, anorexia, gastritis, weight gain, depression, pruritus, vision or taste disturbances, sweating and leucocytosis 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.

OVERDOSAGE

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

EXPIRY DATE

Do not use later than expiry date.

STORAGE

Store below 25^oC, Protected from light.

Keep all medicines out of reach of children.

PRESENTATION

Each Carton of Veloz injection contains Rabeprazole Sodium as white to off white lyophilized powder in a glass vial and 5 ml of sterile water for injection I.P. in a LDPE ampoule.

torrent

Manufactured by :
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