ESOMEPRAZOLE Sodium

ZEMEP

40 mg Powder for Injection (IV)
PROTON PUMP INHIBITOR

FORMULATION:
Each vial contains:
Esomeprazole Sodium equivalent to
Esomeprazole... ..... 40 mg

PRODUCT DESCRIPTION:
A white to off white powder; after reconstitution with sodium chloride intravenous infusion, it forms white to off white coloured clear solution.

PHARMACODYNAMIC PROPERTIES:
Mechanism of Action
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+-ATPase - the acid pump and inhibits both basal and simulated acid secretion.

Pharmacodynamic effects
After 5 days of oral dosing with 20 mg and 40 mg of Esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours respectively, over 24 hours in symptomatic GERD patients. The effect is similar irrespective of whether Esomeprazole is administered orally or intravenously.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown after oral administration of Esomeprazole.

During intravenous administration of 80 mg Esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23.5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours and 11-13 hours, respectively, over 24 hours in healthy subjects.

Healing of reflux esophagitis with Esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumors.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with orally administered Esomeprazole. The findings are considered to be of no clinical significance.

During long-term oral treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infection such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly *Clostridium difficile*.

Pediatric population: Results from the paediatric studies further show that 0.5 mg/kg and 1.0 mg/kg Esomeprazole in <1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intra-esophageal pH <4. The safety profile appeared to be similar to that seen in adults. In a study in pediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or cartinoid tumors.

PHARMACOKINETIC PROPERTIES:
Esomeprazole is rapidly absorbed after oral doses, with peak plasma levels occurring after about 1 to 2 hours. It is acid labile and an enteric-coated formulation has been developed. Bioavailability of Esomeprazole increases with both dose and repeated administration to about 68 and 89% for doses of 20 and 40 mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect of intragastric acidity. Esomeprazole is about 97% bound to plasma proteins. It is extensively metabolized in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxy and desmethyl metabolites, which have no effect on gastric acid section. The remainder is metabolized by the cytochrome P450 isoenzyme CYP3A4 to Esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme. However, there is no accumulation during once daily use. The plasma elimination half-life is about 1.3 hours. Almost 80% of an oral dose is eliminated as metabolites in the urine, the remainder in the feces.

Linearity/Non-linearity
Total exposure (AUC) increases with repeated administration of Esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by inhibition of the CYP2C19 enzyme by Esomeprazole and/or its sulphone metabolite.

Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approximately 13.6 micromol/L. The mean peak plasma concentration after corresponding oral doses is approximately 4.6 micromol/L. A smaller increase (of approximately 30%) can be seen in total exposure after intravenous administration compared to oral administration. There is a dose-linear increase in total exposure following intravenous administration of Esomeprazole as a 30-minute infusion (40 mg, 80 mg or 120 mg) followed by a continuous infusion (4 mg/h or 8 mg/h) over 23.5 hours.

Special Patient Population
Poor metabolizers
Approximately 2.9 ± 1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolizers. In those individuals, the metabolism of Esomeprazole is probably mainly *catalysed* by CYP3A4. After repeated once daily administration of 40 mg oral Esomeprazole, the mean total exposure was approximately 100% higher in poor metabolizers than in subjects with a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%. Similar differences have been seen for intravenous administration of Esomeprazole. These findings have no implications for the posology of Esomeprazole.

Hepatic impairment
The metabolism of Esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the exposure of Esomeprazole. Therefore, maximum dose of 20 mg should not be exceeded in GERD patients with severe dysfunction. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal impairment
No studies have been performed with decreased renal function. The metabolism of Esomeprazole is not expected to be changed in patients with impaired renal function.

Elderly
The metabolism of Esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Pediatric population
In a randomized, open-label, multinational, repeated dose study, Esomeprazole was given as a once-daily 3-minute injection over four days. The study included a total of 59 pediatric patients 0-18 years old of which 50 patients (7 children in the age group 1 to 5 years) completed the study and were evaluated for the pharmacokinetics of Esomeprazole.

The table below describes the systemic exposure of Esomeprazole following the intravenous administration as a 3-minute injection in pediatric patients and adult healthy subjects. The values in the table are geometric means (range). The 20 mg dose for adults was given as a 30-minute infusion. The Css, max was measured 5 minutes post-dose in all pediatric groups and 7 minutes post-dose in adults and after stop of infusion in adults on the 20 mg dose.

Age group	Dose group	AUC (µmol*h/L)	$C_{ss,max}$ (µmol*h/L)
0-1 month*	0.5 mg/kg (n=6)	7.5 (4.5 - 20.5)	3.7 (2.7 - 5.8)
1-11 months*	1.0 mg/kg (n=6)	10.5 (4.5 - 22.2)	8.7 (4.5 - 14.0)
1-5 years	10 mg (n=7)	7.9 (2.9 - 16.6)	9.4 (4.4 - 17.2)
6-11 years	10 mg (n=8)	6.9 (3.5 - 10.9)	5.6 (3.1 - 13.2)
	20 mg (n=8) 20 mg (n=6)**	14.4 (7.2 - 42.3) 10.1 (7.2 - 13.7)	8.8 (3.4 - 29.4) 8.1 (3.4 - 29.4)
12-17 years	20 mg (n=6)	8.1 (4.7 - 15.9)	7.1 (4.8 - 9.0)
	40 mg (n=8)	17.6 (13.1 - 19.8)	10.5 (7.8 - 14.2)
Adults	20 mg (n=22)	5.1 (1.5 - 11.8)	3.9 (1.5 - 6.7)
	40 mg (n=41)	12.6 (4.8 - 21.7)	8.5 (5.4 - 17.9)

* A patient in the age group 0 up to 1 month was defined as a patient with a corrected age of = complete weeks and <44 complete weeks, where corrected age was the sum of the gestational age and the age after birth in complete weeks. A patient in the age group 1 to 11 months had a corrected age of = 44 complete weeks.

**Two patients excluded. 1 most likely a CYP2C19 poor metabolizer and 1 on concomitant treatment with CYP3A4 inhibitor.

Model based predictions indicate that Css, max following intravenous administrations of Esomeprazole as a 10-minute, 20-minute and 30-minute infusions will be reduced by on average 37% to 49%. 54% to 66% and 61% to 72%, respectively, across all age and dose groups compared to when the dose is administered as a 3-minute injection.

INDICATIONS:
Esomeprazole injection is indicated for the short-term treatment (up to 10 days) of GERD (Gastroesophageal Reflux Disease), patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with Esomeprazole Delayed-Release Capsules is not possible or appropriate. For the treatment of peptic ulcer disease and NSAID - associated ulceration in gastroesophageal reflux disease and the Zollinger Ellison Syndrome.

DOSAGE AND ADMINISTRATION:
GERD with a history of Erosive Esophagitis: The recommended adult dose is either 20 or 40 mg Esomeprazole given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 to 30 minutes). Esomeprazole IV for injection should not be administered concomitantly with any other medications through the same intravenous site and or tubing. The intravenous line should always be flushed with either 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, 5% Dextrose Injection, both prior to and after administration of Esomeprazole IV for Injection. Safety and efficacy of Esomeprazole IV for Injection as a treatment of GERD patients with a history or erosive esophagitis for more than 10 days have not been demonstrated.

Geriatric:
No dosage adjustment is necessary.

Renal Insufficiency:
No dosage adjustment is necessary.

Hepatic Insufficiency:
No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of Esomeprazole should not be exceeded.

Gender:
No dosage adjustment is necessary.

CONTRAINDICATIONS:
Hypersensitivity to the active substance Esomeprazole or to other substituted benzimidazoles or to any of the excipients (i.e., disodium edetate, sodium hydroxide) Esomeprazole should not be used concomitantly with Nelfinavir.

SPECIAL PRECAUTIONS:
In the presence of any alarming symptoms (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Esomeprazole may alleviate symptoms and delay diagnosis.
Concomitant administration with Esomeprazole and drugs such as atazanavir and nelfinavir is not recommended.
Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of Esomeprazole and clopidogrel should be avoided.
Some published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with a small increased risk for osteoporosis related fractures. However, in other similar observational studies no such increased risk was found.

Esomeprazole: Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing Esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of Esomeprazole should be considered.
When prescribing Esomeprazole for eradication of *Helicobacter pylori*, possible drug interactions for all components in the triple therapy should be considered.
Clarithromycin is a potent inhibitor of CYP3A4 and hence, contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Granules: This medicinal product contains sucrose and glucose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Effects on ability to drive and use machines:
Esomeprazole is not likely to affect the ability to drive or use machines

PREGNANCY AND LACTATION:
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers: A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE DRUG REACTIONS:
Headache, abdominal pain, constipation, diarrhea, flatulence, nausea, vomiting and injection site reaction.

DRUG INTERACTIONS:
Esomeprazole may interfere with following drugs: Ketoconazole, Itraconazole, Diazepam, Phenytoin, Warfarin, Cisapride, Clarithromycin, Atazanavir, Nelfinavir, Voriconazole, Saquinavir.

OVERDOSE AND TREATMENT:
There have been some reports of overdosage with oral Esomeprazole with dose range up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. No specific antidote for Esomeprazole is known. Since Esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

DIRECTION FOR RECONSTITUTION:
Intravenous Injection (20 or 40 mg) over no less than 3 minutes. The freeze-dried powder should be reconstituted with 5 mL of 0.9% Sodium Chloride Injection. Withdraw 5 mL of the reconstituted solution and administer as an intravenous injection over no less than 3 minutes. The reconstituted solution should be stored at room temperature up to 30°C (86°F) and administered within 12 hours after reconstitution. No refrigeration is required.

CAUTION:
Foods, Drugs, Devices & Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:
10 mL USP Type I Amber Tubular Vial + (diluent) 5 mL Sodium Chloride.

DRP-4015-01
Date of First Authorization: July 7, 2014
Date of Revision of Package Insert: September 13, 2024

Manufactured by:
GUFIC BIOSCIENCES LIMITED
National Highway No.8, Near Grid Kabilpore,
City: Navsari-396 424, Dist: Navsari, Gujarat State, India

Manufactured for:
STALLION LABORATORIES PVT. LTD.
C-1 B, 305/2 & 3 GIDC, Kerala Bavla - 382 220
Dist: Ahmedabad, Gujarat, India

Imported by
AMBICA INTERNATIONAL CORPORATION
9 Amsterdam Extension, Merville Park
Subd., Parañaque City

Distributed by
ZYRE PHARMACEUTICALS CORPORATION
Brgy. 7, Unit 201, ZPC Bldg., Rizal St.
Baño, Legaspi City