Es-Loprot 20mg/40mg I.V. Injection

(Esomeprazole) Lyophilized Powder for Solution: I.V. Injection / I.V. Infusion

ایس۔لوپروٹ ۲۰ ملی گرام/۴۰ ملی گرام آئی وی انجکشن

(ایسومیپرازول) آئی وی انجکشن آئی وی انفیوژن

COMPOSITION: Each vial contains:
Esomeprazole Sodium eq. to Esomeprazole ... 20mg and 40mg. [NQ Specs.]

DESCRIPTION: The active ingredient in **ES-LOPROT I.V. Injection** (Esomeprazole Sodium) is a compound that inhibits gastric acid secretion. Esomeprazole Sodium for Injection is supplied as a sterile, lyophilized, white to off-white powder intended for intravenous administration after reconstitution with 0.9% Sodium chloride Injection, Lactated Ringers Injection or 5% Dextrose Injection. **ES-LOPROT I.V.** (Esomeprazole Sodium) for Injection contains Esomeprazole Sodium 21.3mg and 42.5mg equivalent to Esomeprazole 20mg and 40mg. The stability of Esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.

CLINICAL PHARMACOLOGY: Pharmacokinetics: Absorption: Once daily, administration of Esomeprazole Sodium infusion of 20mg and 40mg over 30 minutes for five days, the results are shown in the following table:

Pharmacokinetic Parameters of Esomeprazole Sodium Following I.V. Dosing for 5 days

Parameter	Esomeprazole Sodium 20mg	Esomeprazole Sodium 40mg
AUC (μmol*h/L)	5.11	16.21
C_{max} (μmol/L)	3.86	7.51
$t_{1/2}$	1.05	1.41

Distribution: Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20μ mol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16L (0.221/kg body weight). **Metabolism:** Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of Esomeprazole lack antisecretory activity. The major part of Esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent upon CYP3A4 which forms the sulphone metabolites. **Excretion:** Esomeprazole is excreted as metabolites primarily in urine but also in feces. Esomeprazole is completely eliminated from plasma and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous Esomeprazole is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous Esomeprazole. **Special Populations:** Investigation of age, gender, race, renal and hepatic impairment and metabolizer status have been made with oral Esomeprazole. The pharmacokinetics of Esomeprazole is not expected to be affected differently by intrinsic or extrinsic factors after intravenous administration compared to oral administration. The same recommendations for dose adjustment in special populations are suggested for intravenous Esomeprazole as for oral Esomeprazole. **Geriatric:** The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary. **Pediatric:** The pharmacokinetics of Esomeprazole has not been studied in patients < 18 years of age. **Gender:** The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary. **Hepatic Insufficiency:** In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency. However, in patients with severe hepatic insufficiency a dose of 20mg once daily should not be exceeded. **Renal Insufficiency:** The pharmacokinetics of Esomeprazole in patients with renal impairment are not expected to be altered related to healthy volunteers as less than 1% of Esomeprazole is excreted unchanged in urine.

PHARMACODYNAMICS: Mechanism of Action: Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+ /K^+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40mg and leads to inhibition of gastric acid secretion.

THERAPEUTIC INDICATIONS: Adults: Esomeprazole Sodium for injection and infusion is indicated for gastric antisecretory treatment when the oral route is not possible, such as: Gastroesophageal reflux disease in patients with Esophagitis or severe symptoms of reflux, Healing of gastric ulcers associated with NSAID therapy, Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers, Prevention of gastric and duodenal ulcer associated with NSAID therapy, in patients at risk. **Children and adolescents aged 1-18 years:** Gastric antisecretory treatment when the oral route is not possible, such as: Gastroesophageal reflux disease (GERD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

DOSAGE AND ADMINISTRATION: Esomeprazole Sodium 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 or 5% Dextrose Injection, both prior to and after administration of Esomeprazole Sodium for injection. The admixture should be stored at room temperature up to 30°C and should be administered within the designated time period as listed in the Table below. No refrigeration is required.

Diluent	Administer within
0.9% Sodium Chloride Injection	12 hours
Lactated Ringers Injection	12 hours
5% Dextrose Injection	6 hours

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. As soon as oral therapy is possible or appropriate, intravenous therapy with Esomeprazole Sodium for injection should be discontinued and the therapy should be continued orally. **GERD with Erosive Esophagitis: Adults:** The recommended adult dose is either 20mg or 40mg Esomeprazole given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes).

Rev: 08-14/2

Size: W: 93 x H: 180 (Leaflet)

Safety and efficacy of Esomeprazole Sodium for injection as a treatment of GERD patients with erosive esophagitis for more than 10 days have not been demonstrated. **Pediatric:** The recommended doses for children ages 1 month to 17 years, inclusive, are provided below. Dose should be infused over 10 minutes to 30 minutes. **1 year to 17 years:** Body weight less than 55kg: 10mg. Body weight 55kg or greater: 20mg. 1 month to less than 1 year of age: 0.5mg/kg.

Preparations for use and administration: Adults: Intravenous Injection (20mg or 40mg vial): The contents of vial should be reconstituted with 5ml of 0.9% Sodium Chloride Injection. Withdraw 5ml of the reconstituted solution and administer an intravenous injection over not less than 3 minutes. **Intravenous Infusion (20mg or 40mg) over 10 minutes to 30 minutes:** A solution for intravenous infusion is prepared by first reconstituting the contents of one vial with 5ml of 0.9% Sodium Chloride Injection, Lactated Ringer's Injection or 5% Dextrose Injection, and further diluting the resulting solution to a final volume of 50ml. The solution (admixture) should be administered as an intravenous infusion over a period of 10 minutes to 30 minutes. The reconstituted solution should be stored up to 30°C and administered within 12 hours after reconstitution. No refrigeration is required. **Pediatric Population: Intravenous Infusion over 10 minutes to 30 minutes (0.5mg/kg) for patients ages 1 month to less than 1 year of age:** A solution for intravenous infusion is prepared by first reconstituting the contents of one vial with 5ml of 0.9% Sodium Chloride Injection, and further diluting the resulting solution to a final volume of 50ml. The resultant concentration after diluting to a final volume of 50ml is as **40mg vial**: 0.8mg/ml, **20mg vial**: 0.4mg/ml. Withdraw appropriate amount of volume for desired dose (0.5mg/kg) and administer as an intravenous infusion over 10 minutes to 30 minutes. **Intravenous Infusion (10mg and 20mg) over 10 minutes to 30 minutes for Pediatric Patients, ages 1 year to 17 years of age: 40mg vial:** A solution for intravenous infusion is prepared by first reconstituting the contents of one vial with 5ml of 0.9% Sodium Chloride Injection, and further diluting the resulting solution to a final volume of 50ml. The resultant concentration after diluting to a final volume of 50ml is 0.8mg/ml. **20mg dose:** Withdraw 25ml of the final solution and administer as an intravenous infusion over 10 minutes to 30 minutes **10mg dose:** Withdraw 12.5ml of the final solution and administer as an intravenous infusion over 10 minutes to 30 minutes **20mg vial:** A solution for intravenous infusion is prepared by first reconstituting the contents of one vial with 5ml of 0.9% Sodium Chloride Injection, and further diluting the resulting solution to a final volume of 50 ml. The resultant concentration after diluting to a final volume of 50ml is 0.4mg/ml. **20mg dose:** Administer the final solution (50ml) as an intravenous infusion over 10 minutes to 30 minutes. **10mg dose:** Withdraw 25ml of the final solution and administer as an intravenous infusion over 10 minutes to 30 minutes.

SIDE EFFECTS: Adverse experiences occurring in >1% of patients treated with Intravenous Esomeprazole are listed below by body system: **Skin and appendages disorders:** Pruritus. **Central and peripheral nervous system disorders**: Dizziness, Headache. **Gastrointestinal system disorders:** Abdominal pain, constipation, diarrhea, dyspepsia , flatulence, dry mouth, nausea. **Respiratory System disorders:** Respiratory infection, sinusitis. **Body as a whole general disorders**: Adverse effects associated with test procedure. **Application site disorders:** Application site reaction (Including mild focal erythema and pruritus at I.V. insertion site). Intravenous treatment with Esomeprazole 20mg and 40mg administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of Esomeprazole 20mg and 40mg.

DRUG INTERACTIONS: Coadministration of oral contraceptives, diazepam, phenytoin or quinidine did not seem to change the pharmacokinetic profile of Esomeprazole. Concomitant administration of Esomeprazole and either (nonselective) or rofecoxib (selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of Esomeprazole or these NSAIDs. Esomeprazole inhibits acid secretion. Therefore, Esomeprazole may interfere with the drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, atazanavir, iron salts, erlotinib and digoxin).

WARNINGS and 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 Injection may alleviate symptoms and delay diagnosis.

PREGNANCY: Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at oral doses up to 280mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Esomeprazole. There are, however, no adequate and well-controlled studies in women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether Esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Esomeprazole Injection should not be used during breast feeding. **Pediatric Use:** The safety and effectiveness of Esomeprazole Sodium for injection have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis. However, effectiveness has not been established in patients less than 1 month of age. **Geriatric Use:** No overall differences in safety and efficacy were observed between the elderly and younger individuals.

OVERDOSE: 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 over dosage, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered.

CONTRA-INDICATIONS: Esomeprazole Injection is contra-indicated in patients with known hypersensitivity to Esomeprazole or to substituted benzimidazoles and nelfinavir.

INSTRUCTIONS: For reconstitution **ES-LOPROT I.V.** 20mg & 40mg Injections, use only 5ml 0.9% Sodium Chloride and discard the remaining solution in ampoule. Store below 30°C. Protect from sunlight & moisture. Keep out of the reach of children.

PRESENTATION: ES-LOPROT I.V. Injection 20mg & 40mg is available as one vial of lyophilized powder for injection with 10ml Ampolue of Sodium Chloride 0.9% injection.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: سلوشن بنانے کے لئے صرف 5ml 0.9% سوڈیم کلورائیڈ استعمال کریں بقیہ ایمپیول میں موجود اضافی مقدار ضائع کردیں۔ 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
NABIQASIM INDUSTRIES (PVT.) LTD.
PHARMA 17/24, Korangi Industrial Area, Karachi-Pakistan.

Rev: 08-14/2

Size: W: 93 x H: 180 (Leaflet)