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Espra® I.V

(Esomeprazole) **40 mg**

Lyophilized Powder for Soultion

Injection

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COMPOSITION:
Each vial contains:
Esomeprazole sodium equivalent to
Esomeprazole ..... 40 mg.

Product Specs.: Innovator

DESCRIPTION:
ESPRA (ESOMEPRAZOLE) I.V for Injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 5 mL vial, intended for intravenous administration after reconstitution with 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP ESPRA (ESOMEPRAZOLE) I.V for Injection contains esomeprazole sodium 42.5 mg equivalent to esomeprazole 40 mg.
The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.

CLINICAL PHARMACOLOGY:
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 40 mg.

PHARMACOKINETICS:
Absorption:
The pharmacokinetic profile of (ESOMEPRAZOLE) I.V for Injection 40 mg was determined in 24 healthy volunteers for the 20 mg dose and 38 healthy volunteers for the 40 mg dose following once daily administration of 20 mg and 40 mg of (ESOMEPRAZOLE) I.V for Injection by constant rate over 30 minutes for five days.

Table 1: Pharmacokinetic Parameters of Esomeprazole Following I.V. Dosing for 5 days.

Parameter	ESPRA 40 mg
AUC (µmol*h/L)	16.21 (14.46:18.16)
(14.46:18.16) C_{max} (µmol/L)	7.51 (6.93:8.13)
t½ (h) (1.30:1.52)	1.41 (1.30:1.52)

Values represent the geometric mean (95% CI)
Distribution: ESPRA is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 µmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.
Metabolism: ESPRA is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of ESPRA lack antisecretory activity. The major part of ESPRA metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.
Following administration of equimolar doses, the S-and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S-than of the R-isomer.
Excretion: ESPRA is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. ESPRA is completely eliminated from plasma, and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous ESPRA is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous ESPRA. During administration of ESPRA over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours plasma clearance (CL) is approximately 5.9 to 7.2 L/h.
Specific Populations:
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: In oral studies on esomeprazole, the AUC and Cmax 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 less than eighteen years of age. Dose adjustments in this group are suggested for intravenous esomeprazole as for oral esomeprazole.
Gender: Dosage adjustment based on gender is not necessary.
Hepatic impairment: In oral studies for esomeprazole, the patients each with mild, moderate and severe liver insufficiency were compared. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency. However, in patients with severe hepatic insufficiency maximum dose of 20 mg once daily should not be exceeded.
Renal impairment: The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

INDICATIONS AND USAGE:
Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis:
ESPRA I.V for Injection is indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively as an alternative to oral therapy when oral ESPRA (ESOMEPRAZOLE) is not possible or appropriate.
Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults:
ESPRA I.V for Injection is indicated for risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults.

DOSAGE AND ADMINISTRATION:
ESPRA I.V 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, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP both prior to and after administration of ESPRA I.V for Injection.
The admixture should be stored at room temperature up to 30ºC (86ºF).and should be administered within the designated time period as listed in Table 1 below.
No refrigeration is required.

Table 2: Storage Time for Final (diluted) Product

Diluent	Administer within
0.9% Sodium Chloride Injection, USP	12 hours
Lactated Ringer's Injection, USP	12 hours
5% Dextrose Injection, USP	6 hours

As soon as oral therapy is possible or appropriate, intravenous therapy should be discontinued and the therapy should be continued orally.
GERD with Erosive Esophagitis:
Adult Patients:
The recommended adult dose is either 20 mg or 40 mg ESPRA given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 to 30 minutes). Safety and efficacy of esomeprazole I.V for Injection for more than 10 days have not been demonstrated.
Dosage adjustment is not required in patients with mild to moderate liver impairment.
For patients with severe liver impairment a maximum dose of 20 mg once daily of ESPRA should not be exceeded

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Pediatric Patients:
The recommended doses for children ages 1 month to 17 years, inclusive, are provided below. Dose should be infused over 10 to 30 minutes.
1 year to 17 years:
- *Body weight less than 55 kg:* 10 mg
- *Body weight 55 kg or greater*: 20 mg
- *1 month to less than 1 year of age:* 0.5 mg/kg

Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults:
Adult dose is 80 mg administered as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/h for a total treatment duration of 72 hours (i.e. includes initial 30-minute dose plus 71.5 hours of continuous infusion). Intravenous therapy is aimed solely at the acute initial management of bleeding gastric or duodenal ulcers and does not constitute full treatment. Intravenous therapy should be followed by oral acid-suppressive therapy.
For patients with liver impairment, no dosage adjustment of the initial ESPRA 80 mg infusion is necessary. For patients with mild to moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of ESPRA 6 mg/h should not be exceeded. For patients with severe liver impairment (Child Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded.

PREPARATION AND ADMINISTRATION INSTRUCTION:
The reconstituted solution of ESPRA esomeprazole I.V should be stored at room temperature up to 30ºC (86ºF) and administered within 12 hours after reconstitution. (Administer within 6 hours if 5% Dextrose Injection is used after reconstitution).
No refigeration is required.

DOSAGE FORMS AND STRENGTHS:
ESPRA (ESOMEPRAZOLE) I.V for Injection is supplied as a freeze-dried white to off-white powder 40 mg of esomeprazole per single-use vial.

CONTRAINDICATIONS:
ESPRA (ESOMEPRAZOLE) I.V is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation.

WARNINGS AND PRECAUTIONS:
In the presence of any alarming symptoms (Significant unintentional weight loss recurrent vomiting, dysphagia, hematemesis and melena) and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with ESPRA injection may alleviate symptoms or delay diagnosis.

ADVERSE REACTIONS:
Adverse Experiences occurring in >1% of population treated with esomeprazole are Headache, Flatulence, Nausea, Abdominal pain, Diarrhea, Mouth dry, Dizziness/vertigo, Constipation injection site reaction include mild focal erythema and pruritus. I.V treatment was found to have a safety profile similar to that of oral administration of esomeprazole 40 mg.

DRUG INTERACTIONS:
ESPRA I.V Esomerprazole may interfere with drugs for which gastric pH affects bioavailability (e.g. ketoconazole, iron salts, erlotinib, digoxin and mycophenolate mofetil). Patients treated with and digoxin may need to be monitored for digoxin toxicity. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomerprazole may reduce the plasma levels of atazanavir, nelfinavir, and saquinavir. Concomitant treatment with a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction.
- ***Clopidogrel:*** Esomerprazole decreases exposure to the active metabolite of clopidogrel.
- ***Tacrolimus:*** Esomerprazole may increase serum levels of tacrolimus.
- ***Methotrexate:*** Esomerprazole may increase serum levels of methotrexate.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
Pregnancy Category C.
There are no adequate and well-controlled studies in pregnant women. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester esomeprazole is this S-Isomer of meprazole use. Oral dose of 40 mg (based on a body surface area basis for a 60 kg person). ESPRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing mothers: Esomeprazole is likely present in human milk. Caution should be exercised when ESPRA I.V is administered to a nursing woman.
Pediatric use: The safety and effectiveness of ESPRA I.V for Injection have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive. However, effectiveness has not been established in patients less than 1 month of age.
Geriatric use: No differences identified in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Hepatic impairment: For adult patients with GERD, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency. For adult patients with mild to moderate liver impairment a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For adult patients with severe liver impairment maximum continuous infusion of 4 mg/h should not be exceeded.

OVERDOSAGE:
Major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia and intermittent clonic convulsions, Confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions. 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. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment Poison control centre should be contacted.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PATIENT COUNSELING INFORMATION:
- Advise patients to let their healthcare provider know if they are taking, or begin taking other medications, because ESPRA can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes.
- Let patients know that antacids may be used while taking ESPRA.
- Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of Clostridium difficile associated diarrhea.
- Advice patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany.

PRESENTATION:
ESPRA I.V Injection 40 mg : 40 mg I.V Injection per single use vial.

بنانے کا طریقہ:
سلوشن بنانے کیلئے صرف ۵ ملی لیٹر 0.9% سوڈیم
کلورائیڈ استعمال کریں بقیہ ایمپیول میں موجود اضافی
مقدار ضائع کر دیں۔

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

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

FOR FURTHER INFORMATION PLEASE CONTACT.

Manufactured for:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

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