1.6.1 Prescribing Information (Summary of products characteristics)

Nabiqasim Industries (Pvt.) Ltd

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

Es-Loprot 40mg IV Injection

The International Non– Proprietary Name (INN): Esomeprazole Sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COMPOSITION:
Each vial contains:
Esomeprazole Sodium eq. to Esomeprazole.....40mg
In house Specs.

For a full list of excipients, see section 6.1.

Description

3. PHARMACEUTICAL FORM:

Injection, A White to off white color cake/powder on reconstitution form clear colorless transparent liquid free from particles and fibers.

4. CLINICAL PARTICULARS:

4.1 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.

4.2 Posology and method of 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).

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.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

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.

Fertility:

Animal studies with the racemic mixture omeprazole, given by oral administration, do not indicate effects with respect to fertility.

4.5 Interaction with other medicinal products and other forms of interaction

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).

4.6 Fertility, pregnancy and lactation:

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.
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Fertility:
Animal studies with the racemic mixture omeprazole, given by oral administration, do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines:

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 Undesirable 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.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Mechanism of Action:
Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.
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.

5.2 Pharmacokinetic properties:

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 (mmol*h/L)	5.11	16.21
C_{max} (mmol/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 2-20m 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.

5.3 Preclinical safety data:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44, and 140.8 mg/kg/day (about 0.35 to 28 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 2.8 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week oral mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 28 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole.

Juvenile Animal Study
A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 57 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Disodium Edetate
Sodium Hydroxide
Water for Injection
Sodium Chloride 0.9% Injection (As diluent)

6.2 Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned in section "4.2. "Posology and method of administration".

6.3 Shelf life:

24months (2Years)

6.4 Special precautions for storage:

Store below 30°C. Protect from sunlight & moisture. Keep out of the reach of children.

6.5 Nature and content of container:

Es-Loprot 40mg IV Injection is supplied as sterile, lyophilized powder in Clear Tubular Glass Vial 10 ml USP Type 1 that contain 40mg Esomeprazole + 1 Ampoule of 10ml Sodium Chloride 0.9% Injection in a single pack.

6.6 Special precautions for disposal and other handling:

Not Applicable

7. MARKETING AUTHORISATION HOLDER (S)

Addresses:
Nabiqasim Industries (Pvt). Ltd.
17/24, Korangi Industrial Area, Korangi, Karachi-Pakistan

8. MARKETING AUTHORISATION NUMBER:

Pakistan:
070679

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION:

First Authorization: 18th August, 2011.
Renewal: 17th August, 2021.

10. DATE OF REVISION OF THE TEXT:

August, 2014