ESOMEGA Infusion 40mg
(ESOMEPRAZOLE INFUSION)

ایس اومیگا انفیوژن
(ایس اومیپرازول انفیوژن)

Lyophilized Powder for solution for Injection/Infusion

4000000027

Each vial of powder for solution for infusion/injection contains Esomeprazole Sodium Ph. Eur., equivalent to 40mg Esomeprazole.

1 DESCRIPTION

The active ingredient in ESOMEGA infusion (esomeprazole sodium) is (S)-5-methoxy-2[[(4-methoxy-3,5- dimethyl-2-pyridinyl)-methyl]sulfinyl]-1 H-benzimidazole sodium, a proton pump inhibitor that inhibits gastric acid secretion.

2 CLINICAL PARTICULARS

2.1 Therapeutic indications

Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

ESOMEGA infusion (esomeprazole sodium) 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 esomeprazole sodium is not possible or appropriate.

Risk Reduction of Re-bleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults

ESOMEGA infusion (esomeprazole sodium) is indicated for risk reduction of re-bleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults.

Gastric antisecretory treatment when the oral route is not possible, such as:

- healing of gastric ulcers associated with NSAID therapy.
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

2.2 Posology and method of administration

ESOMEGA infusion (esomeprazole sodium) 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 ESOMEGA infusion (esomeprazole sodium).

2.2.1 Recommended Dosage in Adults:

GERD with Erosive Esophagitis:

The recommended adult dose is either 20 mg or 40 mg Esomeprazole sodium 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.

Dosage adjustment is not required 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 maximum dose of 20 mg I.V once daily of Esomeprazole sodium should not be exceeded.

Risk Reduction of Re-bleeding 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).

For patients with liver impairment, no dosage adjustment of the initial Esomeprazole 80 mg infusion is necessary. For patients with mild to moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of Esomeprazole 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.

2.2.2 Recommended Dosage in Pediatric Patients:

GERD with Erosive Esophagitis:

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
*Dose should be infused over 10 minutes to 30 minutes.

2.2.3 Method of preparation and administration

Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

Preparation Instructions for Adult Patients:

Intravenous Injection (40 mg vial), The freeze-dried powder should be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP. Withdraw 5 mL of the reconstituted solution and administer as an intravenous injection over no less than 3 minutes.

Preparation Instructions for Pediatric Patients:

Intravenous Infusion (40 mg), A solution for intravenous infusion is prepared by first reconstituting the contents of one vial* with 5 mL of 0.9% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP and further diluting the resulting solution to a final volume of 50 mL. The resultant concentration after diluting to a final volume of 50 mL is 0.8 mg/mL. The solution (admixture) should be administered as an intravenous infusion over a period of 10 minutes to 30 minutes.
*For patients 1 month to less than 1 year of age, first calculate the dose (0.5 mg/kg) to determine the vial size needed.

Risk Reduction of Re-bleeding of Gastric or Duodenal Ulcers in Adults

Preparation Instructions for Loading dose (80 mg) to be given over 30 minutes.

The loading dose of 80 mg is prepared by reconstituting two 40 mg vials. Reconstitute each 40 mg vial with 5 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be further diluted in 100 mL 0.9% Sodium Chloride Injection, USP for intravenous use.

Preparation Instructions for Continuous Infusion to be given at 8 mg/hour for 71.5 hours

The continuous infusion is prepared by using two 40 mg vials. Reconstitute each 40 mg vial with 5 mL each of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be further diluted in 100 mL 0.9% Sodium Chloride Injection, USP for intravenous use

2.3 Contraindication

ESOMEGA infusion (esomeprazole sodium) is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

Esomeprazole should not be used concomitantly with nelfinavir

2.4 WARNINGS AND PRECAUTIONS

2.4.1 Risk of Concomitant Gastric Malignancy

Symptomatic response to therapy with Esomeprazole does not preclude the presence of gastric malignancy.

2.4.2 Atrophic Gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer

2.4.3 Gastrointestinal infections

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter

2.4.4 Absorption of vitamin B12

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

2.4.5 Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs. Discontinue Esomeprazole if acute interstitial nephritis develops.

2.4.6 Clostridium difficile Associated Diarrhea

PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients.

2.4.7 Interaction with Clopidogrel

Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using Esomeprazole, consider alternative anti-platelet therapy.

2.4.8 Risk of fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors.

2.4.9 Hypomagnesaemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

2.4.10 Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Esomeprazole.

2.4.11 Concomitant use of Esomeprazole with St. John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations.

2.4.12 Serious cutaneous adverse reactions (SCARs)

Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been reported very rarely in association with esomeprazole treatment. Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed.

2.4.13 Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements.

2.4.14 Concomitant use of Esomeprazole with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

2.5 USE IN SPECIFIC POPULATIONS

2.5.1 Pregnancy (Category C)

Clinical data on exposed pregnancies with Esomeprazole are insufficient.

2.5.2 Nursing Mothers

It is not known whether esomeprazole is excreted in human breast milk, there is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

2.5.3 Pediatric Use

The safety and effectiveness of Esomeprazole 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.

2.5.4 Geriatric Use

No overall differences in safety and efficacy were observed between the elderly and younger individuals.

2.5.5 Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

2.5.6 Hepatic Impairment

For adult patients with GERD, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). For patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded.

For adult patients with bleeding gastric or duodenal ulcers and liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For adult patients with mild to

moderate liver impairment (Child Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For adult patients with severe liver impairment (Child Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded.

2.6 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (uncommon) have been reported (see section 4.8). If affected patients should not drive or use machines.

2.7 DRUG INTERACTIONS

2.7.1 Protease inhibitors

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

2.7.2 Methotrexate

When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

2.7.3 Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

2.7.4 Medicinal products with pH dependent absorption

With decreased intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole.

2.7.5 Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed.

2.7.6 Phenytoin

Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

2.7.7 Voriconazole

Esomeprazole is an enantiomer of omeprazole. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUC by 15% and 41%, respectively.

2.7.8 Cisapride

Concomitant oral administration of 40 mg esomeprazole and cisapride resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life(t1/2) but no significant increase in peak plasma levels of cisapride.

Warfarin

A few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

2.8 Adverse Reactions

Most common adverse reactions (≥1%) are headache, flatulence, nausea, abdominal pain, injection site reaction, diarrhea, dry mouth, dizziness/vertigo, constipation and pruritus.

2.9 OVERDOSAGE

Single oral doses of 80 mg esomeprazole and intravenous doses of 308 mg esomeprazole over 24 hours were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable.

3 CLINICAL PHARMACOLOGY

3.1 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 stimulated acid secretion.

3.2 Pharmacodynamics

Antisecretory Activity:

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.

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.

Serum Gastrin Effects

In oral studies, the effect of esomeprazole on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy. Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors.

Enterochromaffin-like (ECL) Cell Effects

There are no data available on the effects of intravenous esomeprazole on ECL cells.

Endocrine Effects

Esomeprazole had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of Esomeprazole on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

3.3 Pharmacokinetics

Distribution: The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Metabolism: Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

Elimination: Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent medicinal product is found in urine.

3.3.1 Specific Populations

Renal Impairment:

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

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 total exposure of esomeprazole. Therefore, a 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.

Effects of Age, Body Mass Index, Gender, and Race

Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration. Similar differences have been observed for intravenous administration of esomeprazole.

Geriatric: The metabolism of esomeprazole is not significantly changed in elderly subjects.

Pediatric

In a randomized, open-label, multi-national, repeated dose study, esomeprazole PK was evaluated following a once-daily 3-minute injection in a total of 50 pediatric patients 0 to 17 years old, inclusive. Esomeprazole plasma AUC values for 20 mg Esomeprazole were 183% and 60% higher in pediatric patients aged 6 – 11 years and 12 –17 years respectively compared to adults given 20 mg. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 0.5 mg/kg once daily for pediatric patients 1-11 months of age, 10 mg for pediatric patients 1-17 years with body weight 55 kg would achieve comparable steady-state plasma exposures (AUC 0-24) to those observed in adult patients administered 20 mg of Esomeprazole once every 24 hours. Further, increasing the infusion duration from 3 minutes to 10 minutes or 30 minutes was predicted to produce steady-state C max values that were comparable to those observed in adult patients at the 40 mg and 20 mg Esomeprazole doses.

HOW SUPPLIED:

1 Vial of lyophilized Powder with a 5ml ampoule of 0.9% Sodium Chloride Injection

STORAGE:

Store below 25 °C

INSTRUCTIONS:

Keep away from moisture, heat, light and children.

To be dispensed on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:

BF BIOSCIENCES

BF BIOSCIENCES LIMITED

(A Subsidiary of FEROZSONS LABORATORIES LIMITED)

5 km, Sunder-Raiwind Road,
Raiwind, Lahore, Pakistan.

Mfg. Lic. No. 000655

FEROZSONS LABORATORIES LIMITED