

120.65 mm

181.61 mm

# Esover

Injection / Infusion  
Capsule / Sachet  
(Esomeprazole)

ایسور  
انجکشن / انفیوژن / کپسول / اساشے  
(ایسوپرازول)

## COMPOSITION:

### ESOVER Injection 40mg

Each vial contains:

Esomeprazole (as sodium) Powder for reconstitution ..... 40mg

### (Innovator's Specifications)

### ESOVER Capsule 20mg

Each capsule contains:

Enteric coated pellets of Esomeprazole magnesium trihydrate  
eq. to Esomeprazole.....20mg

### (USP Specifications)

### ESOVER Capsule 40mg

Each capsule contains:

Enteric coated pellets of Esomeprazole magnesium trihydrate  
eq. to Esomeprazole.....40mg

### (USP Specifications)

### ESOVER Sachet 20mg

Each sachet contains:

Enteric coated pellets of Esomeprazole magnesium trihydrate  
eq. to Esomeprazole.....20mg

### (Innovator's Specifications)

### ESOVER Sachet 40mg

Each sachet contains:

Enteric coated pellets of Esomeprazole magnesium trihydrate  
eq. to Esomeprazole.....40mg

### (Innovator's Specifications)

## DESCRIPTION

The active ingredient in ESOVER injection, capsule & sachet is esomeprazole sodium. It inhibits gastric acid secretion more effectively than omeprazole.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H<sup>+</sup>/K<sup>+</sup>-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 40 mg and leads to inhibition of gastric acid secretion.

## INDICATIONS

- Treatment of Gastroesophageal Reflux Disease (GERD)
- Risk Reduction of NSAID-Associated Gastric Ulcer
- H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Triple Therapy (Esover plus amoxicillin and clarithromycin): Esover, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori.
- Pathological Hyper Secretory Conditions Including Zollinger-Ellison Syndrome

## DOSE & ADMINISTRATION

### For injection

- **Short term treatment of GERD with a history of Erosive Esophagitis**
- The recommended adults dose is either 20 or 40mg esomeprazole given once daily by intravenous injection (not less than 3 minutes) or intravenous infusion (10 to 30 minutes) up to 10 days.
- **Healing of gastric ulcers associated with NSAID therapy**
- For healing of gastric ulcers associated with NSAID therapy the usual dose is 20mg once daily.
- **Prevention of gastric and duodenal ulcers associated with NSAID therapy**
- For prevention of gastric and duodenal ulcers associated with NSAID therapy, patients at risk should be treated with 20mg once daily.
- **Hepatic Impairment Patients**
- Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20mg ESOVER IV (Esomeprazole) should not be exceeded.
- **Elderly**
- Dose adjustment is not required in the elderly, instructions for use ESOVER IV (Esomeprazole) 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 0.9% sodium chloride solution for injection, Lactated Ringer's injection or 5% dextrose injection both prior to and after administration of ESOVER IV (Esomeprazole) for injection.

## METHOD OF RECONSTITUTION

### Intravenous Injection (20 or 40mg)

The freeze-dried powder should be reconstituted with 5ml of 0.9% sodium chloride solution for injection. Withdraw 5mL 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 and administered within 12 hours after reconstitution.

### Intravenous Infusion (20 or 40mg)

A solution for intravenous infusion is prepared by first reconstituting the contents of one vial with 5mL of 0.9% sodium chloride solution for injection, Lactated Ringer's injection or 5% dextrose injection and further diluting the resulting solution to a final volume of 100mL. The solution (admixture) should be administered as an intravenous infusion over a period of 10 to 30 minutes.

• 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.

Diluent	Administer within
0.9% Sodium Chloride solution for injection	12 hours
Lactated Ringer's injection	12 hours
Injection 5% Dextrose injection	12 hours

Any unused solution should be discarded.

### For capsule

ESOVER should be taken at least one hour before meals.

### Recommended Dosage Schedule of ESOVER

INDICATION	DOSE	FREQUENCY
<b>Gastroesophageal Reflux Disease (GERD)</b>		
Healing of Erosive Esophagitis	20mg or 40mg	Once Daily for 4 to 8 Weeks
Maintenance of Healing of Erosive Esophagitis	20mg	Once Daily
Symptomatic Gastroesophageal Reflux Disease	20mg	Once Daily for 4 Weeks
<b>Pediatric GERD</b>		
<b>12 to 17 Year Olds</b>		
Healing of Erosive Esophagitis	20mg or 40mg	Once Daily for 4 to 8 Weeks
Symptomatic GERD	20mg	Once Daily for 4 Weeks
<b>1 to 11 Year Olds</b>		
Short-term Treatment of Symptomatic GERD	10mg	Once Daily for up to 8 Weeks
<b>Healing of Erosive Esophagitis</b>		
weight < 20kg	10mg	Once Daily for 8 Weeks
weight = 20kg	10mg or 20mg	Once Daily for 8 Weeks
<b>1 month to &lt;1-year-old</b>		
<b>Erosive esophagitis due to acid-media ted GERD</b>		
weight 3 kg to 5 kg	2.5mg	Once Daily for up to 6 Weeks
weight > 5 kg to 7.5 kg	5mg	Once Daily for up to 6 Weeks
weight > 7.5 kg to 12 kg	10mg	Once Daily for up to 6 Weeks
Risk Reduction of NSAID-Associated Gastric Ulcer	20mg or 40mg	Once Daily for up to 6 months
<b>H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence</b>		
<b>Triple Therapy:</b>		
ESOVER	40mg	Once Daily for 10 Days
Amoxicillin	1000mg	Twice Daily for 10 Days
Clarithromycin	500mg	Twice Daily for 10 Days
Pathologically per Secretory Conditions Including Zollinger-Ellison Syndrome	40mg	Twice Daily

### For Sachet:

- Children 1 – 11 years with a bodyweight of  $\geq 10$  kg
- Gastroesophageal Reflux Disease (GERD)
- Treatment of endoscopically proven erosive reflux esophagitis

- Weight  $\geq 10$  - <20 kg: 10 mg once daily for 8 weeks.
- Weight  $\geq 20$  kg: 10 mg or 20 mg once daily for 8 weeks.
- Symptomatic treatment of gastroesophageal reflux disease (GERD) 10 mg once daily for up to 8 weeks. Doses over 1 mg/kg/day have not been studied.

#### Children over 4 years of age

- Treatment of duodenal ulcer caused by *Helicobacter pylori*
- When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.
- The treatment should be supervised by a specialist.
- The recommended dose is:

Weight	Posology
< 30 kg	Combination with two antibiotics: Esomeprazole 10mg, amoxicillin 25mg/kg body weight and clarithromycin 7.5mg/kg body weight are all administered together twice daily for one week.
30-40 kg	Combination with two antibiotics: Esomeprazole 20mg, amoxicillin 750mg and clarithromycin 7.5mg/kg body weight are all administered together twice daily for one week.
> 40 kg	Combination with two antibiotics: Esomeprazole 20mg, amoxicillin 1g and clarithromycin 500mg are all administered together twice daily for one week.

- Children below the age of 1 year
- The experience of treatment with esomeprazole in infants < 1 year is limited and treatment is therefore not recommended.

#### PHARMACOKINETICS

##### Absorption

After oral administration peak plasma levels (C<sub>max</sub>) occur at approximately 1.5 hours (T<sub>max</sub>). The C<sub>max</sub> increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32  $\mu\text{molh/L}$  on Day 1 to 11.2  $\mu\text{molh/L}$  on Day 5 after 40 mg once daily dosing.

• The AUC after administration of a single 40 mg dose of ESOVER is decreased by 43% to 53% after food intake compared to fasting conditions. ESOVER should be taken at least one hour before meals.

##### Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 22L/kg body weight. Esomeprazole is 97% bound to plasma proteins.

##### Metabolism

Esomeprazole is completely metabolized in the liver 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 hydroxyl 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

Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. 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

##### Hepatic insufficiency

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. Esomeprazole and its major metabolites do not show any tendency to accumulate with once daily dosing.

##### Geriatric

In oral studies, the AUC and C<sub>max</sub> 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 sodium have not been studied in patients <18 years of age.

#### PRECAUTIONS

##### General

In the presence of any alarm symptoms (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

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

##### Hepatic insufficient Patients

Dose reduction in patients with severe hepatic disease should be considered.

##### Renal Insufficient Patients

Patients with severe renal insufficiency should be treated with caution when

administered with esomeprazole IV.

##### Pediatric Patients

The safety and effectiveness of esomeprazole have not been established for pediatric patients.

##### Pregnancy

For esomeprazole, limited data on exposed pregnancies are available. Caution should be exercised when prescribing esomeprazole IV to pregnant women.

##### Nursing Mothers

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore esomeprazole IV should not be used during breastfeeding.

#### SIDE EFFECTS

The following side effects have been reported during therapy of esomeprazole.

##### Common:

Headache, abdominal pain, diarrhea, flatulence, nausea/vomiting, constipation.

##### Uncommon:

Peripheral edema, insomnia, dizziness, paresthesia, somnolence.

##### Rare:

Leukopenia, thrombocytopenia, hypersensitivity reactions e.g., fever, angioedema and anaphylactic reaction/shock, hyponatremia, agitation, confusion, depression, taste disturbance, bronchospasm, stomatitis, gastrointestinal candidiasis, hepatitis with or without jaundice, alopecia, photosensitivity, arthralgia, myalgia, malaise, increased sweating.

##### Very rare:

Aggression, hallucinations, hepatic failure, encephalopathy in patients with pre-existing liver disease, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), muscular weakness, interstitial nephritis, gynecomastia.

#### DRUG INTERACTIONS

• The decreased intra gastric acidity during treatment with esomeprazole might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

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

• Patients treated with proton pump inhibitors and warfarin concomitantly may be monitored for increases in INR and prothrombin time.

#### CONTRAINDICATIONS

- Esomeprazole is contraindicated in patients with known hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients of this medicinal product.
- Esomeprazole, like other PPIs, should not be administered with atazanavir.

#### STORAGE & INSTRUCTIONS

Store between 15-25°C.

Protect from heat, sunlight and moisture. Do not freeze.

Keep out of the reach of children.

To be sold on prescription of a registered medical practitioner only.

#### HOW SUPPLIED

ESOVER Injection 40mg

1 vial + 5ml of 0.9% w/v sodium chloride solution for injection (1x5ml ampoule)

ESOVER Capsule 20mg

14's capsules

ESOVER Capsule 40mg

14's capsules

ESOVER Sachet 20mg

14's sachet

ESOVER Sachet 40mg

14's sachet

خوراک و طریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ گرمی، نمی اور ٹھنڈ ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:

**PHARMASOL**

**PRIVATE LIMITED**

Plot # 549, Sundar Industrial Estate,

Lahore, Pakistan.

PM-0133-00