SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ESOVEL 40 mg, powder and solvent for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40mg of esomeprazole in the form of esomeprazole sodium.

Excipient(s) with known effect: This medicinal product contains less than 1 mmol of sodium (23 mg) per 40 mg, i.e. essentially 'sodium free'.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injectable solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ESOVEL, powder and solvent for injectable solution, is indicated in adults as:

- Gastric antisecretory treatment when the oral route is not possible, for example in:

  - Gastroesophageal reflux disease (GERD) in patients with esophagitis and/or severe reflux symptoms,

  - the healing of gastric ulcers associated with the use of NSAIDs,

  - the prevention of gastroduodenal ulcers associated with the use of NSAIDs, in at-risk patients.

- Prevention of recurrent bleeding after therapeutic endoscopy for a bleeding gastric or duodenal ulcer.

ESOVEL, powder and solvent for injectable solution, is indicated in children and adolescents aged 1 to 18 years as:

- Gastric antisecretory treatment when the oral route is not possible, for example in:

  - gastroesophageal reflux (GERD) in patients with erosive reflux esophagitis and/or severe reflux symptoms.

4.2. Posology and method of administration

Posology

Adults

Gastric antisecretory treatment when the oral route is not possible.
Patients unable to take the medication orally may be treated parenterally, at a dosage of 20 to 40 mg once daily.
In patients with reflux esophagitis, the recommended dose is 40 mg once daily. In patients treated for symptomatic reflux, the recommended dose is 20 mg once daily.
For the healing of gastric ulcers associated with NSAID use: 20 mg once daily. For the prevention of gastroduodenal ulcers associated with NSAID use in at-risk patients: 20 mg once daily.
Usually, the duration of intravenous treatment is short and the switch to oral administration should be made as soon as possible.
Prevention of recurrent bleeding from a gastric or duodenal ulcer.
Following therapeutic endoscopy for a bleeding gastric or duodenal ulcer, a dose of 80 mg should be administered as a bolus by intravenous infusion over 30 minutes, followed by a continuous intravenous infusion of 8 mg/h for 3 days (72 hours).
Parenteral treatment must be followed by oral antisecretory treatment.

Method of administration

For instructions on reconstituting the medicinal product before administration, see section 6.6.
Injection

- 40 mg dose

5 ml of the reconstituted solution (8 mg/ml) should be administered by intravenous injection over at least 3 minutes.

- 20 mg dose

2.5 ml or half of the reconstituted solution (8 mg/ml) should be administered by intravenous injection over at least 3 minutes. Any unused solution should be discarded.
Infusion

- 40 mg dose

The reconstituted solution should be administered by intravenous infusion over 10 to 30 minutes.

- 20 mg dose

Half of the reconstituted solution should be administered by intravenous infusion over 10 to 30 minutes. Any unused solution should be discarded.

- 80 mg bolus dose

The reconstituted solution should be administered as a continuous intravenous infusion over 30 minutes.

- Dose of 8 mg/h

The reconstituted solution should be administered as a continuous intravenous infusion over a period of 71.5 hours (calculated infusion rate of 8 mg/h, see section 6.3 for the shelf life of the reconstituted solution).

Specific populations

Kidney failure

No dosage adjustment is necessary in case of renal insufficiency.
Due to limited experience in patients with severe renal impairment, ESOVEL should be used with caution in these patients (see section 5.2).

Liver failure

GERD: No dose adjustment is necessary in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the maximum dose of 20 mg of ESOVEL should not be exceeded (see section 5.2).
Bleeding ulcer: No dose adjustment is necessary in patients with mild to moderate hepatic impairment. For patients with severe hepatic impairment, after an initial bolus of 80 mg of ESOVEL for infusion, a dose of 4 mg/h as a continuous intravenous infusion administered over 71.5 hours may be sufficient (see section 5.2).

Elderly subjects

No dosage adjustment is necessary in elderly patients.

Pediatric population

Dosage

Children and adolescents aged 1 to 18 years

Gastric antisecretory treatment when the oral route is not possible

Patients who cannot take medication orally may be treated parenterally once daily for part of the total duration of treatment for GERD (see doses in the table below).
Generally, the duration of intravenous treatment should be short and the switch to oral treatment should be made as soon as possible.

Recommended doses of esomeprazole for intravenous administration

Age	Treatment of erosive reflux esophagitis	Treatment of reflux (GERD) symptoms
1-11 years old	Weight < 20 kg: 10 mg once a day Weight ≥ 20 kg: 10 mg or 20 mg once a day	10 mg once a day
12-18 years old	40 mg once a day	20 mg once a day

Method of administration

For instructions on reconstituting the medicinal product before administration, see section 6.6.

Injection

40 mg dose

5 ml of the reconstituted solution (8 mg/ml) should be administered as an intravenous injection over at least 3 minutes.

20 mg dose

2.5 ml or half of the reconstituted solution (8 mg/ml) should be administered as an intravenous injection over at least 3 minutes. Any unused solution should be discarded.

10 mg dose

1.25 ml of the reconstituted solution (8 mg/ml) should be administered as an intravenous injection over at least 3 minutes. Any unused solution should be discarded.

Infusion

40 mg dose

The reconstituted solution should be administered by intravenous infusion over 10 to 30 minutes.

20 mg dose

Half of the reconstituted solution should be administered by intravenous infusion over 10 to 30 minutes. Any unused solution should be discarded.

10 mg dose

One quarter of the reconstituted solution should be administered by intravenous infusion over 10 to 30 minutes. Any unused solution should be discarded.

4.3. Contraindications

- Hypersensitivity to the active substance, to benzimidazole derivatives or to any of the excipients listed in section 6.1.

- Esomeprazole should not be used concomitantly with nelfinavir (see section 4.5).

4.4. Special warnings and precautions for use

In the presence of any of the following alarm symptoms (such as significant and involuntary weight loss, repeated vomiting, dysphagia, hematemesis or melena) or in the presence or suspicion of a gastric ulcer, the possibility of a malignant lesion should be excluded because ESOVEL may mask symptoms and delay diagnosis.

Gastrointestinal infections

Treatment with PPIs may slightly increase the risk of gastrointestinal infections due to germs such as *Salmonella* and *Campylobacter* (see section 5.1).

Vitamin B12 absorption

Like all drugs aimed at decreasing gastric acid secretion, esomeprazole may decrease the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria.
This should be taken into account during long-term treatment in patients with reduced vitamin B12 reserves or risk factors leading to decreased absorption of vitamin B12.

Hypomagnesemia

Cases of severe hypomagnesemia have been reported in patients treated with proton pump inhibitors (PPIs) such as esomeprazole for at least three months, and in most cases for one year. Hypomagnesemia can manifest with serious clinical signs such as fatigue, tetany, delirium, seizures, dizziness, and ventricular arrhythmia, but it can also begin

insidiously and go unnoticed. In most patients, hypomagnesemia improved after magnesium supplementation and discontinuation of the PPI.
In patients requiring prolonged treatment or in cases of PPIs being combined with digoxin or with drugs that can induce hypomagnesemia (e.g., diuretics), measurement of blood magnesium levels should be considered by healthcare professionals before starting PPI treatment and then regularly during treatment.

Risk of fractures

Proton pump inhibitors (PPIs), particularly when used at high doses and for prolonged periods (> 1 year), may moderately increase the risk of hip, wrist, and vertebral fractures, primarily in elderly patients or in the presence of other identified risk factors. Observational studies suggest that PPIs may increase the overall fracture risk by 10% to 40%. This increase may be partly attributable to other risk factors. Patients at risk of osteoporosis should be managed according to current guidelines and receive appropriate vitamin D and calcium supplementation.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very rare cases of subacute cutaneous lupus erythematosus (SCLE). If lesions develop, particularly on sun-exposed areas of the skin, and are accompanied by joint pain, the patient should consult a doctor promptly, and the healthcare professional should consider discontinuing ESOVEL. The occurrence of SCLE after treatment with one proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medications

The combination of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is considered essential, close clinical monitoring is recommended, along with increasing the atazanavir dose to 400 mg with 100 mg of ritonavir; a maximum dose of 20 mg of esomeprazole should not be exceeded.
Esomeprazole is a CYP2C19 inhibitor. At the start or end of treatment with esomeprazole, the risk of interactions with drugs metabolized by CYP2C19 should be considered. An interaction between clopidogrel and esomeprazole has been observed (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be avoided.

Severe adverse skin reactions (SCARs)

Severe adverse skin reactions (SCARs) such as erythema multiforme (EP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN or Lyell's syndrome), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been very rarely reported in association with esomeprazole therapy.
Patients should be informed of the clinical signs or symptoms suggestive of such serious skin reactions and should consult their doctor immediately if these signs or symptoms are observed.
In the event of suggestive clinical signs, treatment with esomeprazole should be stopped immediately and appropriate medical treatment and close monitoring should be implemented.
Patients who have experienced such an episode of severe skin reaction should never again be exposed to esomeprazole.

Interference with laboratory tests

An increase in Chromogranin A (CgA) concentration may interfere with investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be discontinued for at least 5 days before CgA measurement (see section 5.1). If CgA and gastrin levels have not normalized after the initial measurement, the measurements should be repeated 14 days after discontinuation of proton pump inhibitor therapy.

4.5. Interactions with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors

Interactions between omeprazole and certain protease inhibitors have been reported. The clinical significance and mechanism of these interactions are not always known. The increase in gastric pH observed during omeprazole treatment may alter the absorption of protease inhibitors. Other interaction mechanisms exist, including inhibition of CYP2C19.
For atazanavir and nelfinavir, decreased plasma concentrations have been reported when used in combination with omeprazole; therefore, concomitant administration of omeprazole and these drugs is not recommended. Omeprazole

(40 mg once daily) administered in combination with atazanavir 300 mg and ritonavir 100 mg in healthy volunteers resulted in a substantial decrease in atazanavir plasma concentrations (approximately a 75% decrease in AUC, Cmax, and Cmin). Increasing the atazanavir dose to 400 mg did not compensate for the effect of omeprazole on atazanavir plasma concentrations.
The combination of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg in healthy volunteers decreased atazanavir exposure by approximately 30% compared to the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily administered alone. The combination with omeprazole (40 mg once daily) decreased the mean AUC, Cmax, and Cmin of nelfinavir by 36–39% and the mean AUC, Cmax, and Cmin of its pharmacologically active metabolite M8 by 75–92%.
Due to the similarity of the pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration of esomeprazole and atazanavir is not recommended (see section 4.4), and concomitant administration of esomeprazole and nelfinavir is contraindicated (see section 4.3).
For saquinavir (in combination with ritonavir), an increase in plasma concentration (80-100%) has been reported when used in combination with omeprazole (40 mg once daily). Treatment with omeprazole 20 mg once daily did not alter exposure to darunavir (in combination with ritonavir) or to amprenavir (in combination with ritonavir).
Treatment with esomeprazole 20 mg once daily did not alter amprenavir exposure (with or without ritonavir). Treatment with omeprazole 40 mg once daily did not alter lopinavir exposure (with ritonavir).

Methotrexate

Increased methotrexate concentrations have been observed in some patients when methotrexate is administered concomitantly with proton pump inhibitors (PPIs). When high doses of methotrexate are administered, temporary discontinuation of esomeprazole treatment may be necessary.

Tacrolimus

Increased serum tacrolimus concentrations have been observed during concomitant administration with esomeprazole. Close monitoring of tacrolimus concentrations and renal function (creatinine clearance) should be performed, and the tacrolimus dosage should be adjusted if necessary.

Medications whose absorption is pH-dependent

Inhibition of gastric acidity during treatment with esomeprazole and other PPIs could decrease or increase drug absorption if this is dependent on gastric pH.
As with other drugs that decrease intragastric acidity, the absorption of certain drugs, such as ketoconazole, itraconazole, and erlotinib, may be decreased, while the absorption of drugs such as digoxin may increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two of ten subjects). Digoxin toxicity has been rarely reported. However, particular care should be taken when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should therefore be intensified.

Drugs metabolized by CYP2C19

Esomeprazole inhibits CYP2C19, the main enzyme responsible for its metabolism. Therefore, when administered concomitantly with drugs metabolized by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin, etc., plasma concentrations of these drugs may be increased, and a dose reduction may be necessary. This should be particularly considered when esomeprazole is prescribed for on-demand treatment.
No in vivo interaction studies have been performed with high doses of intravenous ESOVEL at a dosage of 80 mg followed by 8 mg/h. The effect of esomeprazole on drugs metabolized by CYP2C19 may be more pronounced during this treatment, and patients should be closely monitored for adverse effects during the three-day intravenous treatment period.

Diazepam

Concomitant administration of 30 mg of esomeprazole orally and diazepam results in a 45% decrease in the clearance of diazepam, which is metabolized by CYP2C19.

Phenytoin

The concomitant administration of 40 mg of oral esomeprazole and phenytoin leads to a 13% increase in plasma phenytoin concentrations in epileptic patients. It is recommended to monitor plasma phenytoin concentrations when initiating or discontinuing esomeprazole treatment.

Voriconazole

Omeprazole (at a dose of 40 mg once daily) resulted in increased plasma concentrations of voriconazole (a CYP2C19 substrate), with Cmax and AUCτ increased by 15% and 41% respectively.

Cilostazol

Like omeprazole, esomeprazole is a CYP2C19 inhibitor. In a crossover study, omeprazole, administered at a dose of 40 mg to healthy subjects, increased the Cmax and AUC of cilostazol by 18% and 26% respectively, and of one of its active metabolites by 29% and 69% respectively.

Cisapride

In healthy volunteers, concomitant administration of 40 mg of esomeprazole and cisapride resulted in a 32% increase in the area under the plasma concentration-time curve (AUC) and a 31% prolongation of the elimination half-life (t1/2) without a significant increase in the peak plasma concentration of cisapride. The slight prolongation of the QTc interval observed after administration of cisapride alone was not exacerbated by concomitant administration of cisapride with esomeprazole.

Warfarin

A clinical trial showed that when 40 mg of esomeprazole was administered orally to patients treated with warfarin, coagulation times remained within normal limits. However, since marketing, a few cases of clinically significant INR elevation have been reported during concomitant treatment. Monitoring is recommended at the start and end of concomitant treatment with esomeprazole and warfarin or other coumarin derivatives.

Clopidogrel

Results from studies in healthy subjects showed a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose followed by a 75 mg daily maintenance dose) and esomeprazole (40 mg/day orally), resulting in an approximately 40% decrease in exposure to the active metabolite of clopidogrel and an approximately 14% decrease in maximum inhibition of platelet aggregation (induced by ADP).
In a study of healthy subjects, a decrease in exposure of approximately 40% to the active metabolite of clopidogrel was observed when a fixed-dose combination of esomeprazole 20 mg and acetylsalicylic acid (ASA) 81 mg was administered with clopidogrel compared to clopidogrel alone. However, the peak levels of ADP-induced platelet aggregation inhibition in these patients were identical in the clopidogrel group and the clopidogrel + fixed-dose combination (esomeprazole + acetylsalicylic acid) group.
Conflicting data on the clinical consequences of a PK/PD interaction with esomeprazole in terms of major cardiovascular events have been reported in both observational and clinical studies. As a precaution, concomitant use of clopidogrel should be avoided.

Drugs studied with no clinically significant interaction

Amoxicillin or quinidine

Esomeprazole has no clinically significant effect on the pharmacokinetics of amoxicillin or quinidine.

Naproxen or rofecoxib

Short-term studies evaluating concomitant administration of esomeprazole with naproxen or rofecoxib have not shown any clinically significant pharmacokinetic interaction.

Effects of other drugs on the pharmacokinetics of esomeprazole.

Drugs that inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolized by CYP2C19 and CYP3A4.
Concomitant administration of esomeprazole with a CYP3A4 inhibitor, clarithromycin (500 mg twice daily) leads to a doubling of the area under the curve (AUC) of esomeprazole.
Concomitant administration of esomeprazole and a combined CYP2C19 and CYP3A4 inhibitor may result in a more than double increase in the Cmax and AUC of esomeprazole.
Voriconazole, an inhibitor of CYP2C19 and CYP3A4, resulted in a 280% increase in the AUCt of omeprazole .
A systematic adjustment of the esomeprazole dose is not necessary in either of these situations.
However, dose adjustment should be considered in patients with severe hepatic impairment, and if long-term treatment is indicated.

Drugs that induce CYP2C19 and/or CYP3A4

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased serum levels of esomeprazole by increasing esomeprazole metabolism.

Pediatric population

Interaction studies have only been conducted in adults.

4.6. Fertility, pregnancy and breastfeeding

Pregnancy

Clinical data on pregnancies exposed to ESOVEL are insufficient.
Data from epidemiological studies on a large number of pregnancies exposed to omeprazole, a racemic mixture, have revealed no malformative or fetotoxic effects.
Animal studies with esomeprazole have not revealed any direct or indirect malformative or embryonic/fetal effects.
Animal studies with the racemic mixture have not shown any direct or indirect harmful effects with respect to pregnancy, parturition, or postnatal development. ESOVEL should be prescribed with caution during pregnancy.
A moderate amount of data in pregnant women (between 300 and 1000 pregnancies) has not shown any malformative or toxic effects on the fetus or newborn due to esomeprazole.
Animal studies have not shown any direct or indirect harmful effects on reproduction (see section 5.3)

Breastfeeding

It is not known whether esomeprazole is excreted in breast milk. There are insufficient data on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breastfeeding.

Fertility

Animal studies with a racemic mixture of omeprazole, administered orally, do not indicate any effects on fertility.

4.7. Effects on the ability to drive vehicles and use machinery

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

4.8. Undesirable effects

Security Profile Summary
Headache, abdominal pain, diarrhea, and nausea are among the reactions most frequently reported in clinical trials (and also during post-marketing use). Furthermore, the safety profile is similar across different formulations, treatment indications, age groups, and patient populations. No dose-related adverse reactions have been identified.
Table of side effects
The following adverse reactions have been reported or suspected during clinical trials of esomeprazole administered orally or intravenously, and since its marketing with oral administration. None of the effects were dose-dependent. Adverse reactions are classified by frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Classes Organ Systems	**Frequency**	**Side effect**
Hematological and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions such as fever, angioedema, anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon:	Peripheral edema
	Rare	Hyponatremia.
	Frequency not known	Hypomagnesemia (see section 4.4); severe hypomagnesemia may be associated with hypocalcemia. Hypomagnesemia may also be associated with hypokalemia.

Classes Organ Systems	Frequency	Side effect
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Disorders of the nervous system	Frequent	Headaches
	Uncommon	Dizziness, paresthesia, drowsiness
	Rare	Taste disturbances
Eye conditions	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Dizziness
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Frequent	Abdominal pain, constipation, diarrhea, flatulence, nausea/vomiting, benign polyps of the fundic glands
	Uncommon	Dry mouth.
	Rare	Stomatitis, gastrointestinal candidiasis
	Frequency not known	microscopic colitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Liver failure, encephalopathy in patients with pre-existing liver failure
Skin and subcutaneous tissue disorders	Frequent	Reactions to the administration site*
	Uncommon	Dermatitis, itching, rash, hives
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (or Lyell's syndrome), drug reaction with eosinophilia and systemic symptoms (or DRESS)
	Undetermined	Subacute cutaneous lupus erythematosus (see section 4.4).
Musculoskeletal and systemic disorders	Uncommon	Fracture of the hip, wrist or vertebrae (see section 4.4)
	Rare	Arthralgia, myalgia
	Very rare	Muscle weakness
Kidney and urinary tract disorders	Very rare	Interstitial nephritis; in some patients, renal failure has been reported concomitantly.
Disorders of reproductive functions and the breast	Very rare	Gynecomastia
General disorders and administration site abnormalities	Rare	Discomfort, increased sweating

*Reactions at the administration site were mainly observed in a study with exposure to high doses for 3 days (72 hours) (see section 5.3).
Cases of irreversible visual impairment, including blindness, have been described in an isolated number of patients with severe deterioration of their general condition who received omeprazole (the racemic form) intravenously, mainly at high doses, without a causal link having been established.

Pediatric population

A multinational, open-label, randomized study was conducted to evaluate the pharmacokinetics of repeated intravenous doses of esomeprazole once daily for 4 days in pediatric patients aged 0 to 18 years (see section 5.2). A total of 57 patients (8 children aged 1 to 5 years) were included in the safety assessment. The safety results are consistent with the known safety profile of esomeprazole, and no new safety signals were identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals should report any suspected adverse reactions using the FRILAB reporting form available under the pharmacovigilance tab of the website: www.frilab.ch

4.9. Overdose

To date, experience with intentional overdose is very limited. Symptoms described following oral administration of a 280 mg dose include gastrointestinal symptoms and signs of fatigue. Single oral doses of 80 mg daily and intravenous doses of 308 mg of esomeprazole over 24 hours have been well tolerated. There is no known specific antidote. Esomeprazole is highly protein-bound and therefore not readily dialyzable. In case of overdose, treatment will be symptomatic, and general supportive measures should be implemented.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Drugs for acid-related disorders, PROTON PUMP INHIBITOR, ATC code: A02BC05
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Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specifically targeted mechanism of action. It is a specific inhibitor of the proton pump in the parietal cell. The two R- and S-isomers of omeprazole have similar pharmacodynamic activity.

Mechanism of action

Esomeprazole is a weak base. It is concentrated and converted to its active form in the acidic environment of the secretory canaliculi of parietal cells, where it inhibits the H+K+-ATPase enzyme (the proton pump), basal acid secretion, and stimulated acid secretion.

Pharmacodynamic effects

After 5 days of oral administration of 20 mg and 40 mg esomeprazole, an intragastric pH greater than 4 was maintained for an average of 13 and 17 hours out of 24, respectively, in patients with symptomatic gastroesophageal reflux disease (GERD). The effects are similar whether esomeprazole is administered orally or intravenously.
Using the area under the curve (AUC) as a parameter reflecting plasma concentration, a relationship between inhibition of gastric acid secretion and the area under the curve (AUC) was demonstrated after oral administration of esomeprazole.
In healthy volunteers, during intravenous administration of an 80 mg esomeprazole bolus over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23.5 hours, an intragastric pH greater than 4 and an intragastric pH greater than 6 were maintained on average for 21 hours and 11–13 hours out of 24 hours, respectively.
Healing of reflux esophagitis with esomeprazole 40 mg is achieved in approximately 78% of patients after 4 weeks and in 93% of patients after 8 weeks of treatment.
In a randomized, double-blind, placebo-controlled clinical trial, patients with endoscopically confirmed peptic ulcer bleeding (Forrest Ia, Ib, IIa, or IIb, representing 9%, 43%, 38%, and 10% of patients, respectively) were randomized to receive ESOVEL, solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg of esomeprazole as a 30-minute intravenous infusion followed by a continuous infusion of 8 mg/h for 72 hours, or placebo. After the initial 72-hour period, all patients received open-label 40 mg of ESOVEL orally for 27 days to reduce acid secretion. The incidence of recurrent bleeding within 3 days was 5.9% in the ESOVEL group, compared to 10.3% in the placebo group. After 30 days of treatment, the incidence of recurrent bleeding in the ESOVEL group was 7.7% versus 13.6% in the placebo group.
During treatment with antisecretory drugs, serum gastrin levels increase in response to decreased acid secretion. CgA also increases due to the decrease in gastric acidity. The elevated CgA concentration can interfere with the results of tests for neuroendocrine tumors. According to published data, proton pump inhibitor (PPI) use should be discontinued between 5 days and 2 weeks before measuring CgA levels. The aim is to allow CgA levels, which may have been artificially elevated by PPI use, to return to normal.
An increase in the number of ECL cells, possibly related to increased serum gastrin concentrations, was observed in both children and adults receiving long-term esomeprazole treatment. These findings are considered to have no clinical significance.
During long-term oral treatment with antisecretory drugs, gastric glandular cysts have been reported with a slightly increased frequency. These changes, which are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.
Decreased gastric acid secretion, regardless of the cause, including that induced by proton pump inhibitors (PPIs), increases the amount of bacteria normally present in the digestive tract within the stomach. PPI treatment may slightly increase the risk of gastrointestinal infections caused by organisms such as *Salmonella* and *Campylobacter* , and possibly by *Clostridium difficile,* in hospitalized patients.

Pediatric population

In a placebo-controlled study (98 patients aged 1–11 months), efficacy and tolerability were evaluated in patients with signs and symptoms of GERD. Esomeprazole 1 mg/kg once daily was administered orally for 2 weeks (open-label phase), and 80 patients were enrolled for an additional 4 weeks (double-blind, discontinuation phase). There was no significant difference between esomeprazole and placebo for the primary endpoint (time to discontinuation of treatment for worsening of symptoms).
In a placebo-controlled study (52 patients under 1 month of age), efficacy and tolerability were evaluated in patients with GERD symptoms. Esomeprazole 0.5 mg/kg once daily was administered orally for a minimum of 10 days. There was no significant difference between esomeprazole and placebo for the primary endpoint (change in the number of GERD symptom episodes compared to baseline).
Results from pediatric studies also show that esomeprazole 0.5 mg/kg and 1 mg/kg, in infants aged less than 1 month and between 1-11 months, reduces the average percentage of time spent with an intra-esophageal pH < 4.
The tolerance profile appears similar to that observed in adults.
In a study conducted in a pediatric population (children aged less than 1 year to 17 years) with GERD and receiving long-term PPI therapy, 61% of children had low levels of ECL cell hyperplasia with no known clinical significance and without development of atrophic gastritis or carcinoid tumors.

5.2. Pharmacokinetic properties

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg. Esomeprazole is 97% bound to plasma proteins.

Biotransformation

Esomeprazole is completely metabolized by cytochrome P450 (CYP).
The majority of its metabolism is dependent on the polymorphic enzyme CYP2C19, responsible for the formation of the hydroxy and desmethyl metabolites of esomeprazole. The remaining portion is dependent on another specific isoenzyme, CYP3A4, responsible for the formation of esomeprazole sulfone, the main plasma metabolite.

Elimination

The parameters below primarily reflect pharmacokinetics in individuals with a functional CYP2C19 enzyme or who are said to be "rapid metabolizers".
Total plasma clearance is approximately 17 L/h after a single dose and approximately 9 L/h after repeated administrations. The plasma elimination half-life is approximately 1.3 hours after repeated once-daily administration.
Esomeprazole is completely eliminated from the plasma between two administrations with no tendency to accumulate when taken once a day.
The main metabolites of esomeprazole do not affect gastric acid secretion. Approximately 80% of an orally administered dose of esomeprazole is eliminated as metabolites in the urine, with the remainder found in the feces. Less than 1% of the parent drug is recovered in the urine.

Linearity/non-linearity

The area under the plasma concentration-time curve (AUC) increases with repeated administrations of esomeprazole. This increase is dose-dependent and results in a greater-than-dose-proportional increase in the AUC after repeated administrations. This time- and dose-dependent effect is due to a decrease in first-pass metabolism and systemic clearance, probably caused by inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulfone metabolite.
Following repeated intravenous administration of 40 mg doses, the mean peak plasma concentration is approximately 13.6 µmol/l. The mean peak plasma concentration following oral administration of identical doses is approximately 4.6 µmol/l.
A smaller increase (of about 30%) in total exposure may be observed after intravenous administration compared to oral administration.
Following intravenous administration of esomeprazole (40 mg, 80 mg or 120 mg) as a 30-minute infusion followed by a continuous infusion (4 mg/h or 8 mg/h) for 23.5 hours, there is an increase in total exposure proportional to the administered dose.

Specific populations

Slow metabolizers

Approximately 2.9 ± 1.5% of the population are deficient in a functional CYP2C19 enzyme and are referred to as "poor metabolizers." In these individuals, the metabolism of esomeprazole is likely catalyzed primarily by CYP3A4. Following repeated administration of a 40 mg oral dose of esomeprazole daily, the mean total exposure is approximately 100%

higher in poor metabolizers than in subjects with a functional CYP2C19 enzyme (extensive metabolizers). The mean peak plasma concentration is increased by approximately 60%.
Similar differences were observed with intravenous administration of esomeprazole. These observations do not affect the dosage of esomeprazole.

Gender

Following oral administration of a single 40 mg dose of esomeprazole, the mean total exposure is approximately 30% higher in women compared to men. No sex differences were observed after repeated daily administration of esomeprazole. Similar differences were observed with intravenous administration of esomeprazole. These findings have no implications for the esomeprazole dosage.

Liver failure

The metabolism of esomeprazole may be altered in patients with mild to moderate hepatic impairment.
The rate of metabolism is reduced in patients with severe hepatic impairment, resulting in a doubling of total esomeprazole exposure. Therefore, a maximum dose of 20 mg should not be exceeded in GERD patients with severe hepatic impairment.
For patients with a bleeding ulcer who have severe hepatic impairment, after an initial bolus of 80 mg, a maximum dose of 4 mg/h by continuous intravenous infusion administered for 71.5 hours may be sufficient.
Esomeprazole and its main metabolites do not show a tendency to accumulate with a single daily dose.

Kidney failure

No studies have been conducted in patients with impaired renal function.
Since the kidney is responsible for eliminating esomeprazole metabolites but not the parent molecule, esomeprazole metabolism is not altered in patients with renal impairment.

Elderly subjects

The metabolism of esomeprazole is not significantly altered in elderly subjects (71-80 years).

Pediatric population

In a multinational, randomized, open-label, repeat-dose study, esomeprazole was administered as a 3-minute injection once daily for 4 days. This study included a total of 59 pediatric patients aged 0 to 18 years, of whom 50 (7 children aged 1 to 5 years) completed the study to evaluate the pharmacokinetics of esomeprazole.
The table below describes systemic exposure to esomeprazole following 3 minutes of intravenous administration in pediatric patients and healthy adult subjects.
The values in this table are the geometric means (extreme values).
The 20 mg dose for an adult was administered as a 30-minute infusion.
The Css, max was measured 5 minutes after administration in all pediatric groups and 7 minutes after administration in adults at the 40 mg dose and after stopping the infusion in adults at the 20 mg dose.

Age	**Dose**	**ASC (µmol*h/l)**	**$C_{ss,max}$ (µmol/l)**
0-1 month*	0.5 mg/kg (n=6)	7.5 (4.5-20.5)	3.7 (2.7-5.8)
1-11 months*	1.0 mg/kg (n=6)	10.5 (4.5-22.2)	8.7 (4.5-14.0)
1-5 years	10 mg (n=7)	7.9 (2.9-16.6)	9.4 (4.4-17.2)
6-11 years old	10 mg (n=8)	6.9 (3.5-10.9)	5.6 (3.1-13.2)
	20 mg (n=8) 20mg (n=6) **	14.4 (7.2-42.3) 10.1 (7.2-13.7)	8.8 (3.4-29.4) 8.1 (3.4-29.4)
12-17 years old	20 mg (n=6)	8.1 (4.7-15.9)	7.1 (4.8-9.0)
	40 mg (n=8)	17.6 (13.1-19.8)	10.5 (7.8-14.2)
Adults	20 mg (n=22)	5.1 (1.5-11.8)	3.9 (1.5-6.7)
	40 mg (n=41)	12.6 (4.8-21.7)	8.5 (5.4-17.9)

A patient in the 0-1 month age group was defined as a patient with a corrected age ≥32 completed weeks and <44 completed weeks, where corrected age was the sum of gestational age and age after birth and was expressed in completed weeks. A patient in the 1-11 month age group had a corrected age ≥44 completed weeks.
** Two patients were excluded: a probable slow metabolizer of CYP2C19 and a patient who was taking concomitant treatment with a CYP 3A4 inhibitor.
Predictive models indicate that Css,max after intravenous administration of esomeprazole in 10-minute, 20-minute and 30-minute infusions will be reduced on average by approximately 37% to 49%, 54% to 66% and 61% to 72%, respectively, in all age groups and dose groups compared to the dose administered by injection over a 3-minute period.

5.3. Preclinical safety data

Non-clinical studies have not revealed any special hazard for humans, based on conventional safety pharmacology studies of repeated-dose toxicity, genotoxicity, carcinogenic potential, reproductive toxicity, and developmental toxicity. The following adverse reactions were not observed in clinical studies but were observed in animals at exposure levels similar to those used in humans and may have clinical significance, detailed below:
Oral carcinogenicity studies in rats with the racemic mixture showed hyperplasia of gastric ECL cells and carcinoid tumors. In rats, these gastric changes result from prolonged and significant hypergastrinemia, secondary to reduced gastric acid secretion, and are observed in this animal during long-term treatment with acid secretion inhibitors.
In the preclinical program using the intravenous formulation of esomeprazole, no vessel irritation was observed, but a mild tissue inflammatory reaction at the injection site after subcutaneous (perivenous) injection was observed (see section 4.8).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Solvent: Water for injection.

6.2. Incompatibilities

This medicine should not be mixed with other medicines, except those mentioned in section 6.6.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store at a temperature not exceeding 30°C.
Store in the original packaging, away from light.

6.5. Nature and contents of container

Powder in a bottle (glass) + 5 ml of solvent in an ampoule (LDPE).
Box containing 1 bottle and ampoule.

6.6. Special precautions for disposal and handling

The reconstituted solution must be visually inspected for particulate matter and discoloration before administration. Only a clear solution should be used.
For single use only.
If not all of the reconstituted solution in the bottle is required, any unused solution should be disposed of in accordance with applicable regulations.
IV injection 40 mg
The solution for IV injection (8mg/ml) is prepared by adding 5 ml of a 0.9% sodium chloride solution for intravenous use to the vial of esomeprazole 40 mg.
The reconstituted IV injection solution is clear and colorless to very pale yellow.
Infusion 40 mg
The solution for infusion is prepared by dissolving the contents of one vial of esomeprazole 40 mg in 100 ml of a 0.9% sodium chloride solution for intravenous use.
Infusion 80 mg
The solution for infusion is prepared by dissolving the contents of two vials of esomeprazole 40 mg in 100 ml of a 0.9% sodium chloride solution for intravenous use.
The reconstituted infusion solution is clear and colorless to very pale yellow.

7. MARKETING AUTHORISATION HOLDER AND OPERATOR

FRILAB SA
17 RUE DES PIERRES DU NITON
1207 GENEVA - SWITZERLAND

8. MANUFACTURER

SKYMAP PHARMACEUTICALS PVT. LTD
B-2, DEV BHOOMI INDUSTRIAL ESTATE, PUHANA IQBALPUR ROAD,
ROORKE 247667 DISTT. HARIDWAR, UTTARAKHAND - INDIA

9. DATE OF REVISION OF THE TEXT

February 2026.

10. DOSIMETRY

Not applicable.

11. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List II