SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ESOVEL 20 mg, gastro-resistant capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg of esomeprazole (as esomeprazole magnesium dihydrate).

Excipient(s) with known effect: sucrose, sodium benzoate (E211).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant capsule.
Capsule with an opaque yellow cap and an opaque yellow body imprinted in black with "20 mg". The capsule contains off-white to greyish spherical microgranules .

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ESOVEL capsules are indicated in adults for:

- Gastroesophageal reflux disease (GERD)
  - Treatment of erosive reflux esophagitis.
  - Maintenance treatment and prevention of relapses after healing of esophagitis due to gastroesophageal reflux.
  - Symptomatic treatment of gastroesophageal reflux disease (GERD).
- In combination with appropriate antibiotic therapy, eradication of Helicobacter pylori for:
  - healing of duodenal ulcers in cases of *Helicobacter pylori infection* and,
  - prevention of recurrence of gastro-duodenal ulcer in case of *Helicobacter pylori infection* .
- Patients in whom non-steroidal anti-inflammatory drug (NSAID) treatment must be continued:
  - Healing of gastric ulcers associated with the use of NSAIDs.
  - Prevention of gastroduodenal ulcers associated with NSAID use in at-risk patients.
- Continuation of oral treatment after intravenous prevention of hemorrhagic recurrence of a gastroduodenal ulcer.
- Treatment of Zollinger-Ellison syndrome.

ESOVEL capsules are indicated for adolescents from the age of 12 years for:

- Gastroesophageal reflux disease (GERD)
  - Treatment of erosive reflux esophagitis.
  - Maintenance treatment and prevention of relapses after healing of esophagitis due to gastroesophageal reflux.
  - Symptomatic treatment of gastroesophageal reflux disease (GERD)
- In combination with antibiotics in the treatment of duodenal ulcer due to Helicobacter pylori.

4.2. Posology and method of administration

Oral route.

Posology

Adults

Gastroesophageal reflux disease (GERD):

Treatment of erosive reflux esophagitis

40 mg once a day for 4 weeks.

An additional 4 weeks of treatment is recommended for patients whose esophagitis has not healed or whose symptoms persist.

Maintenance treatment and prevention of recurrence after healing of gastroesophageal reflux esophagitis

20 mg once a day.

Symptomatic treatment of gastroesophageal reflux disease (GERD)

20 mg once daily in patients without esophagitis. If symptoms persist after 4 weeks, further investigations may be necessary. After symptomatic resolution, ESOVEL 20 mg once daily, administered as needed, helps control symptomatic recurrences. In patients treated with an NSAID who are at risk of developing a peptic ulcer, on-demand administration is not recommended for subsequent symptom control.

In combination with appropriate antibiotic therapy, eradication of *Helicobacter pylori* for:

- healing of duodenal ulcers in cases of *Helicobacter pylori infection* and,
- Prevention of recurrence of gastroduodenal ulcer in case of *Helicobacter pylori infection* : 20 mg of ESOVEL combined with amoxicillin 1 g and clarithromycin 500 mg, all twice a day for 7 days.

Patients in whom non-steroidal anti-inflammatory drug (NSAID) treatment must be continued

- Healing of gastric ulcers associated with NSAID use: the usual dose is 20 mg once daily. The duration of treatment is 4 to 8 weeks.
- Prevention of gastroduodenal ulcers associated with NSAID use in at-risk patients: 20 mg once daily.

Continuation of oral treatment after intravenous prevention of recurrent bleeding from a gastroduodenal ulcer
40 mg once daily for 4 weeks following intravenous prevention of recurrent bleeding from a gastroduodenal ulcer.
Treatment of Zollinger-Ellison syndrome
The recommended starting dose is 40 mg of ESOVEL twice daily. Dosage should be individually adjusted and treatment continued for as long as clinically necessary. Based on available clinical data, the majority of patients are controlled with doses between 80 and 160 mg of esomeprazole per day. For doses above 80 mg per day, the daily dose should be divided and administered in two doses.

Specific populations

Kidney failure
No dose adjustment is necessary in patients with renal impairment. 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
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. The maximum dose of 20 mg of ESOVEL should not be exceeded in patients with severe hepatic impairment (see section 5.2).
elderly subjects
No dosage adjustment is necessary in elderly patients.

Pediatric population

Teenagers from the age of 12

Gastroesophageal reflux disease (GERD):

- Treatment of erosive reflux esophagitis

40 mg once a day for 4 weeks.

An additional 4 weeks of treatment is recommended for patients whose esophagitis has not healed or whose symptoms persist.

- Maintenance treatment and prevention of recurrence after healing of gastroesophageal reflux esophagitis

20 mg once a day.

• Symptomatic treatment of gastroesophageal reflux disease (GERD)

20 mg once daily in patients without esophagitis. If symptoms persist after 4 weeks, further investigations may be necessary. After symptomatic resolution, a 20 mg once-daily dose is sufficient to control symptomatic recurrences.

Treatment of duodenal ulcer due to Helicobacter pylori infection:
When choosing which antibiotics to use, it will be necessary to take into account official national, regional and local recommendations regarding bacterial resistance, the duration of treatment (most often 7 days, but this duration can sometimes reach 14 days), and the appropriate use of these antibiotics.
The treatment will need to be monitored by a specialist.
The recommended dosage is as follows:

Weight	Dosage
30-40 kg	Combination with two antibiotics: ESOVEL 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered simultaneously twice daily for 1 week.
> 40 kg	Combination with two antibiotics: ESOVEL 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered simultaneously twice a day for 1 week.

Children under 12 years old

ESOVEL should not be used in children under 12 years of age due to a lack of available data.

Method of administration

The capsules should be swallowed whole with a drink. They should not be chewed or crushed. For patients who have difficulty swallowing, the capsules can also be opened and their contents dispersed in half a glass of still water. No other liquid should be used, as the gastro-enteric coating may dissolve. Stir and drink the solution with the granules immediately or within 30 minutes. Rinse the glass with half a glass of water and drink it. The granules should not be chewed or crushed.
For patients unable to swallow, the contents of the capsules can be dispersed in still water and administered via a gastric tube. It is important to ensure beforehand that the chosen tube and syringe are suitable. For preparation and administration via gastric tube, refer to section 6.6.

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 event of suspicion or presence of a gastric ulcer, the possibility of a malignant lesion must be excluded because treatment with ESOVEL may alleviate symptoms and delay diagnosis.

Long-term use
Patients receiving maintenance therapy (and those, in particular, treated for more than a year) should be monitored regularly.

On-demand processing
Patients receiving on-demand treatment should be advised of the need to contact their doctor if their symptoms change.

Eradication of *Helicobacter pylori*
When prescribing esomeprazole for Helicobacter *pylori eradication* , potential drug interactions of all components of the eradication therapy must be considered. Clarithromycin is a potent CYP3A4 inhibitor; therefore, its contraindications and interactions must be taken into account when eradication therapy is administered concomitantly with drugs metabolized by CYP3A4, such as cisapride .

Gastrointestinal infections
Treatment with a proton pump inhibitor 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 that reduce gastric acid secretion, esomeprazole can 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 stores or risk factors leading to decreased vitamin B12 absorption.

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 PPI combination 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 SLE. 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 SLE after treatment with a proton pump inhibitor may increase the risk of SLE with other proton pump inhibitors.

Combinations 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.
When prescribing esomeprazole treatment on demand, the impact on interactions with other drugs should be taken into consideration due to fluctuations in plasma concentrations of esomeprazole (see section 4.5).

Severe adverse skin reactions (SCARs)
Severe adverse skin reactions (SCARs) such as erythema multiforme (EP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal , have been reported in very rare cases in association with esomeprazole treatment.
Patients should be informed of the clinical signs and symptoms of severe skin reactions EP/SSJ/TEN/DRESS and consult their doctor immediately if they observe them.
Esomeprazole should be stopped immediately if signs and symptoms of severe skin reactions occur, and close monitoring/ additional medical care should be provided as needed.

Treatment should not be restarted in patients with PE/SJS/TEN/ DRESS. Interference with laboratory tests
An increase in Chromogranin A (CgA) concentration may interfere with tests for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be stopped 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 stopping proton pump inhibitor treatment.

Excipients
This medicine contains sucrose. Its use is not recommended in patients with fructose intolerance, glucose and galactose malabsorption syndrome, or sucrase/isomaltase deficiency.
Sodium benzoate may increase the risk of jaundice (yellowing of the skin and eyes) in newborns (up to 4 weeks).
This medicine contains less than 1 mmol (23 mg) of sodium per capsule, that is to say it is essentially “sodium-free.”

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 without omeprazole.
The combination of 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 exposure to amprenavir (with or without 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 may decrease or increase drug absorption if this is dependent on gastric pH. As with other drugs that decrease intragastric acidity, the absorption of some drugs, such as ketoconazole , itraconazole , and erlotinib , may be decreased, while the absorption of drugs such as digoxin may increase during esomeprazole treatment. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin (from 10% 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.

Diazepam

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

Phenytoin

Concomitant administration of 40 mg of esomeprazole 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 substrate of CYP2C19), with Cmax and AUC τ 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 leads to a 32% increase in the area under the plasma concentration 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 is not increased when cisapride is administered concomitantly with esomeprazole (see section 4.4).

Warfarin

A clinical trial showed that when 40 mg of esomeprazole was administered 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 (loading dose of 300 mg/maintenance dose of 75 mg daily) and esomeprazole (40 mg/day orally), resulting in a decrease of approximately 40% in exposure to the active metabolite of clopidogrel and a decrease of approximately 14% in the 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 maximum 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 observed in both observational and clinical studies. As a precaution, concomitant use of clopidogrel should be avoided.

Drugs studied with no clinically significant interaction

Amoxicillin and 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 the CYP3A4 inhibitor clarithromycin (500 mg twice daily) results in a doubling of the area under the curve (AUC) of

esomeprazole. Concomitant administration of esomeprazole with a combined CYP2C19/CYP3A4 inhibitor may result in a more than twofold increase in esomeprazole exposure.
Voriconazole, a CYP2C19 and CYP3A4 inhibitor, resulted in a 280% increase in the AUC οφ omeprazole. Routine dose adjustment of esomeprazole 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. 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 racemic mixture have not revealed any malformative or fetotoxic effects . Animal studies with esomeprazole have not revealed any direct or indirect malformative effects with respect to embryonal/fetal development. 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 (rare) 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 undesirable effects

The following adverse reactions have been reported or suspected during clinical trials of esomeprazole and since its marketing. None of the effects were dose-dependent. Adverse reactions are classified by frequency: very common >1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥1/10000 to <1/1000; very rare <1/10000; not known (cannot be estimated from the available data).

Organ System Classes	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.
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	Rare	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	failure , encephalopathy in patients with pre-existing liver failure
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, itching, rash, hives
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (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.
Diseases of the reproductive organs and breast	Very rare	Gynecomastia

General disorders and administration site abnormalities	Rare	Discomfort, increased sweating

Reporting 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 report any adverse effects suspected unwanted substance via the FRILAB declaration form available under the tab Pharmacovigilance information from the website: www.frilab.ch

4.9. Overdose

To date, experience with intentional overdose is very limited. Symptoms described following a 280 mg dose include gastrointestinal symptoms and signs of weakness. Single doses of 80 mg per day 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 aimed at preserving vital functions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Drugs for acid-related disorders, proton pump inhibitor, ATC code: A02BC05
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

Following oral administration of 20 and 40 mg of esomeprazole, the antisecretory effect appears within one hour. After repeated administration of 20 mg of esomeprazole once daily for 5 days, the maximum acid output obtained after pentagastrin stimulation is reduced by an average of 90% on the 5th ^{day}, 6 to 7 hours after administration.
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. The percentages of patients with a pH > 4 for at least 8, 12, and 16 hours were 76%, 54%, and 24%, respectively, with 20 mg esomeprazole, and 97%, 92%, and 56% with 40 mg esomeprazole.
Using the area under the curve (AUC) as a parameter reflecting plasma concentration, a relationship between inhibition of gastric acid secretion and exposure was demonstrated.
Healing of reflux esophagitis with esomeprazole 40 mg is achieved in approximately 78% of patients after 4 weeks of treatment and in 93% of patients after 8 weeks of treatment.
One week of treatment with esomeprazole 20 mg twice daily combined with appropriate antibiotics results in the eradication of *Helicobacter pylori* in approximately 90% of patients.
antisecretory monotherapy to achieve healing and disappearance of symptoms in the case of uncomplicated duodenal ulcer.
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 esomeprazole 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, or placebo, for 72 hours. After the initial 72-hour period, all patients received 40 mg of esomeprazole orally as an open-label treatment for 27 days to reduce acid secretion. The occurrence of recurrent bleeding within 3 days was 5.9% in the esomeprazole-treated group, compared to 10.3% in the placebo group.
After 30 days of treatment, the occurrence of recurrent bleeding in the esomeprazole-treated group was 7.7% versus 13.6% in the placebo group.
During treatment with antisecretory drugs , serum gastrin levels increase in response to the reduction in gastric acid secretion. CgA also increases due to the decrease in gastric acidity. Elevated CgA levels 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 treatment with antisecretory drugs , gastric glandular cysts have been reported with a slightly increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion; they 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.

Clinical efficacy

In two studies versus ranitidine, used as an active comparator, better efficacy with esomeprazole was demonstrated in the healing of gastric ulcers in patients treated with NSAIDs, including selective COX-2 inhibitors.
In two studies versus placebo, used as comparator, better efficacy with esomeprazole was demonstrated in the prevention of gastroduodenal ulcers in patients treated with NSAIDs (age > 60 years and/or history of ulcer), including selective COX-2 inhibitors.

Pediatric population

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

Absorption

Esomeprazole is unstable in acidic environments. It is administered orally as gastro-resistant granules. *In vivo* , conversion to the R isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma concentrations occurring approximately 1 to 2 hours after administration. Absolute bioavailability is 64% after a single 40 mg dose and increases to 89% after repeated once-daily administration. The corresponding values for 20 mg of esomeprazole are 50% and 68%, respectively.
Food intake delays and decreases the absorption of esomeprazole, although this does not have a significant influence on the antisecretory effect of esomeprazole.

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, which is responsible for the formation of the hydroxy and desmethyl metabolites of esomeprazole. The remaining portion is dependent on another specific isoenzyme , CYP3A4, which is 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 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 dosing. Esomeprazole is completely eliminated from the plasma between doses with no tendency to accumulate when administered once daily.

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 pharmacokinetics of esomeprazole have been studied at doses up to 40 mg twice daily. 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-dependent 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.

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 40 mg of esomeprazole once daily, the mean area under the plasma concentration-time curve (AUC) 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%. These observations do not affect the dosage of esomeprazole.

Gender

Following administration of a single 40 mg dose of esomeprazole, the mean area under the plasma concentration-time curve (AUC) is approximately 30% higher in women compared to men. No sex differences were observed after repeated daily 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 decreased in patients with severe hepatic impairment, resulting in a doubling of the area under the plasma concentration-time curve (AUC) of esomeprazole. Therefore, a maximum dose of 20 mg should not be exceeded in patients with severe hepatic impairment. Esomeprazole and its major metabolites do not show a tendency to accumulate with once-daily dosing.

Kidney failure

No studies have been conducted in patients with impaired renal function. Since the kidneys are responsible for eliminating esomeprazole metabolites but not the parent molecule, no alteration in esomeprazole metabolism is expected in patients with renal impairment.

Elderly subjects

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

Pediatric population

Adolescents aged 12-18:
Following repeated administration of 20 mg and 40 mg doses of esomeprazole, the total exposure (AUC) and time to peak plasma concentrations (tmax) in children aged 12 to 18 years are similar to those observed in adults with both doses of esomeprazole.

5.3. Preclinical safety data

Non-clinical studies have not revealed any special hazard for humans, based on conventional studies of safety pharmacology, 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:

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 rats during long-term treatment with acid secretion inhibitors.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule contents :

Hypromellose , sugar sphere, polysorbate 80, dimethicone emulsion 35% (dimethicone , polysorbate 20, sodium benzoate (E211)), mannitol 25, Eudragit L30 D55, diacetyl monoglyceride , purified talc, triethyl citrate, Gelucire 50/13

Capsule shell :

Gelatin, methylparaben , propylparaben , sodium lauryl sulfate , titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at a temperature not exceeding 25°C. Store in the original packaging, away from moisture.

6.5. Nature and contents of container

Box of 14 gastro-resistant 20 mg capsules in blister packs (aluminium/aluminium).

6.6. Special precautions for disposal and handling

Administration via gastric tube:

1. Place the contents of one capsule into a suitable syringe and fill the syringe with approximately 25 ml of fluid and 5 ml of air. For some feeding tubes, a volume of 50 ml of water is required to disperse the granules and prevent blockage of the tube.
2. Immediately shake the syringe for about 2 minutes to disperse the granules.
3. Hold the syringe tip in the air and check that the tip is not obstructed by the dispersion.
4. Connect the syringe to the probe while maintaining the position described above.
5. Shake the syringe, then position it with the tip pointing downwards. Immediately inject 5-10 ml into the probe. Then reposition the syringe with the tip pointing upwards and shake it (the syringe must be held with the tip pointing upwards to prevent the tip from clogging).
6. Invert the syringe tip downwards and immediately inject another 5-10 ml into the probe. Repeat this operation until the syringe is empty.
7. Refill the syringe with 25 ml of water and 5 ml of air and repeat step 6, if necessary, to ensure no residue remains in the syringe. For some probes, a volume of 50 ml of water is required.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

Special precautions for disposal

No special requirements.

7. OPERATOR

FRILAB SA
17, rue des Pierres du Niton

1207 Geneva
SWISS

8. MANUFACTURER

Athena Drug Delivery Solutions Pvt. Ltd.
A-1 to A-5, MIDC, Chemical Zone,
Ambernath (W), District Thane-421501

9. DATE OF REVISION OF THE TEXT

October 2024

10. DOSIMETRY

Not applicable

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List II