Esamal

(Esomeprazole)

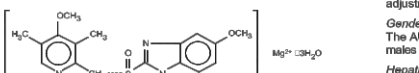
ایسامال

(ایسومیپرازول)

Capsules 20mg, 40mg

DESCRIPTION

ESAMAL capsules are an enteric-coated pellet formulation of esomeprazole magnesium due to its acid labile nature. Esomeprazole is the S-isomer of omeprazole, which is mixture of the S- and R- isomers which inhibits gastric acid secretion more effectively than omeprazole. Chemically it is bis(5-methoxy-2-[(S)-[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. The molecular formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$ and the structural formula is:



Esomeprazole magnesium trihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

ESAMAL (Esomeprazole) is available for oral administration as:

1. ESAMAL Capsules 20mg
   Each capsule contains:
   Enteric-coated pellets of Esomeprazole
   magnesium trihydrate equivalent to
   Esomeprazole ... 20mg
2. ESAMAL Capsules 40mg
   Each capsule contains:
   Enteric-coated pellets of Esomeprazole
   magnesium trihydrate equivalent to
   Esomeprazole ... 40mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

Pharmacokinetics

Absorption

After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} 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 40mg.

At repeated once-daily dosing with 40mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40mg.

Effect of food: The AUC after administration of a single 40mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on the intragastric acidity.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20µmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazoles metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining part is dependent on CYP3A4 which forms the sulphone metabolite.

Excretion

Total plasma clearence is about 17L/h after a single dose and about 9L/h after repeated administration. The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of the parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Special Populations

Geriatric

The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dose adjustment based on age is not necessary.

Gender

The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dose adjustment based on gender is not necessary.

Hepatic Insufficiency

In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dose adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20mg once daily should not be exceeded.

Renal Insufficiency

The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers, as less than 1% of esomeprazole is excreted unchanged in urine.

THERAPEUTIC INDICATIONS

ESAMAL (Esomeprazole) is indicated for:

1. **Treatment of Gastroesophageal Reflux Disease (GERD)**
   - Healing of Erosive Esophagitis
   - Maintenance of Healing of Erosive Esophagitis
   - Symptomatic Gastroesophageal Reflux Disease
2. **Risk Reduction of NSAID-Associated Gastric Ulcer**
3. **H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**
   - As a triple therapy (Esomeprazole plus amoxicillin and clarithromycin) is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

Note: In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

4. **Pathological Hypersecretory Conditions including Zollinger Ellison Syndrome**

DOSAGE AND ADMINISTRATION

The recommended adult dosages are outlined in the table below. ESAMAL (Esomeprazole) capsules should be swallowed whole and taken at least one hour before meals.

Recommended Adult Dosage Schedule

Indication	Dose	Frequency
I. Gastroesophageal Reflux Disease (GERD)		
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 (If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered).
II. Risk Reduction of NSAID-Associated Gastric Ulcer	20mg or 40mg	Once Daily for up to 6 months
III. H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (Triple Therapy):		
ESAMAL	40mg	Once Daily for 10 Days
Amoxicillin	1000mg	Twice Daily for 10 Days
Clarithromycin	500mg	Twice Daily for 10 Days
IV. Pathological Hypersecretory Conditions including Zollinger-Ellison Syndrome	40mg	Twice Daily

Pediatric (12 to 17 year Olds)		
Indication	Dose	Frequency
I. Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20mg or 40mg	Once Daily for 4 to 8 weeks
Symptomatic GERD	20mg	Once Daily for 4 weeks

For patients with severe liver impairment (Child Pugh Class C), a dose of 20mg of ESAMAL (Esomeprazole) should not be exceeded.

ADVERSE REACTIONS

The following adverse drug reactions have been reported during therapy of esomeprazole.

Common: Headache, abdominal pain, constipation, diarrhea, flatulence and nausea/vomiting.

Uncommon: Peripheral oedema, insomnia, dizziness, paraesthesia, somnolence, vertigo, dry mouth, increased liver enzymes, dermatitis, pruritus, rash, urticaria, fracture of the hip and wrist or spine.

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

CONTRAINDICATIONS

- Esomeprazole is contraindicated in patients with known hypersensitivity to Proton Pump Inhibitor or substituted benzimidazoles or any excipient of the product.
- Esomeprazole should not be used concomitantly with nelfinavir.

PRECAUTIONS

General

- Symptomatic response to therapy with Esomeprazole does not preclude the presence of gastric malignancy.
- Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.
- Proton pump inhibitor may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients.
- Proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), monitoring magnesium levels prior to initiation of PPI treatment and periodically is required.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Esomeprazole should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions

- Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance.
- Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.
- 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 due to decreased intragastric acidity during treatment with esomeprazole.
- Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising 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.
- Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumors.
- Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.
- Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin.
- Avoid concomitant use of Esomeprazole with clopidogrel, St John's Wort, or rifampin.
- Concomitant administration of PPIs and methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate.

OVERDOSAGE

Symptoms

The symptoms with deliberate overdose are transient. Single doses of 80 mg of esomeprazole were uneventful.

Treatment

No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

STORAGE

Store below 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

ESAMAL (Esomeprazole) Capsules 20mg are available in blister pack of 14's.
ESAMAL (Esomeprazole) Capsules 40mg are available in blister pack of 14's.

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

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں یا تفصیلی
ہدایات کیلئے ڈبے کے اندر موجود پرچہ ملاحظہ کریں۔
ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔

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