

SUMMARY OF PRODUCT CHARACTERISTICS

1- Name of the medicinal product

Esomelodan (esomeprazole 40mg enteric coated tablets)

2- Qualitative and quantitative composition:

Each enteric coated tablet contains 44.6mg esomeprazole magnesium trihydrate equivalent to 40mg esomeprazole.

For the full list of excipients, see section 6.1

3- Pharmaceutical form:

Enteric coated tablet

4- Clinical Particulars:

4.1 therapeutic indications:

Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

ESOMELODAN is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 weeks course of ESOMELODAN may be considered.

Maintenance of Healing of Erosive Esophagitis

ESOMELODAN is indicated to maintain symptom resolution and healing of erosive esophagitis.

Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

ESOMELODAN is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children 1 year or older.

Risk Reduction of NSAID-Associated Gastric Ulcer

ESOMELODAN is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (> 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

H. pylori

Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy (ESOMELODAN plus amoxicillin and clarithromycin): ESOMELODAN, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. Triple Therapy (ESOMELODAN plus amoxicillin and clarithromycin): ESOMELODAN, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

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.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

ESOMELODAN is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

4.2 posology and method of administration

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

Adults and adolescents from the age of 12 years

Gastroesophageal Reflux Disease (GERD)

- Treatment of erosive reflux esophagitis

40 mg once daily for 4 weeks.

An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.

- Long-term management of patients with healed esophagitis to prevent relapse

20 mg once daily.

- Symptomatic treatment of gastroesophageal reflux disease (GERD)

20 mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. In adults, an on demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

Adults

In combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* and

- healing of *Helicobacter pylori* associated duodenal ulcer and

- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers: 20 mg Esomeprazole with 1 g. amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy

- healing of gastric ulcers associated with NSAID therapy: The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

- prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk: 20 mg once daily.

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is Esomeprazole 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Children below the age of 12 years

Esomeprazole should not be used in children younger than 12 years since no data is available.

Impaired renal function

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution.

Impaired hepatic function

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg Esomeprazole should not be exceeded.

Elderly

Dose adjustment is not required in the elderly.

4.3 contraindications

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation. Esomeprazole like other PPIs should not be administered with atazanavir.

4.4 special warnings and special precautions for use

Concurrent Gastric Malignancy

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

Atrophic Gastritis

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

Risks of Amoxicillin (as Part of *H. pylori* Triple Therapy)

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions that have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis”. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Risks of Clarithromycin (as Part of *H. pylori* Triple Therapy)

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, terfenadine, ergotamine, or dihydroergotamine is contraindicated.

Bone Fracture

“Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term

PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.”

* Prescription proton pump inhibitor (PPI) drugs may cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year), magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.

* Low serum magnesium levels can result in serious adverse events including muscle spasm (tetany), irregular heartbeat (arrhythmias), and convulsions (seizures); however, patients do not always have these symptoms. Treatment of hypomagnesemia generally requires magnesium supplements. Treatment in patients taking a PPI and who have hypomagnesemia may also require stopping the PPI.

4.5 Interactions

Effects of esomeprazole on the pharmacokinetics of other drugs

Medicinal products with pH dependent absorption

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

Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg / ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. PPIs including esomeprazole should not be co-administered with atazanavir. (See section contraindications).

Drugs metabolised by CYP2C19 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. This should be considered especially when prescribing esomeprazole for on demand therapy. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC.

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t_{1/2}) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (See section special warnings and special precautions for use).

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Omeprazole acts as an inhibitor of CYP 2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69% respectively. Co-administration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above-mentioned active metabolite. Therefore, a dose reduction of cilostazol from 100 mg b.i.d. to 50 mg b.i.d. should be considered.

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine. Studies evaluating concomitant administration of esomeprazole and naproxen did not identify any clinically relevant pharmacokinetic interactions during short term studies.

Effects of other drugs on the pharmacokinetics of esomeprazole

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

4.6 Pregnancy and lactation

For esomeprazole, clinical data on exposed pregnancies are insufficient. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effects. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

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

4.7 effects on ability to drive and use machines

No effects have been observed.

4.8 undesirable effects

Body as a Whole: abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; Cardiovascular: flushing, hypertension, tachycardia; Endocrine: goiter; Gastrointestinal: bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; Hearing: earache, tinnitus; Hematologic: anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; Hepatic: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; Metabolic/Nutritional: glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; Musculoskeletal:

arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; Nervous System/Psychiatric: anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; Reproductive: dysmenorrhea, menstrual disorder, vaginitis; Respiratory: asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; Skin and Appendages: acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; Special Senses: otitis media, parosmia, taste loss, taste perversion; Urogenital: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; Visual: conjunctivitis, vision abnormal.

4.9 overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5-Pharmacological properties:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proton pump inhibitor, Atc Code: A02BC05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Site and mechanism of action

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H⁺K⁺-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Therapeutic effects of acid inhibition

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of H. pylori in approximately 90% of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

Other effects related to acid inhibition

During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion. An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs. In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

5.2 Pharmacokinetic properties

Absorption and distribution

Esomeprazole is acid labile and is administered orally as enteric-coated. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% plasma protein bound.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism and excretion

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

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

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

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d.

The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time - and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Special patient populations

Approximately 2.9–1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole. The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age). Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

Impaired organ function

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

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

Paediatric

Adolescents 12-18 years:

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (T_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose
Methocel E5 LV premium
Croscarmellose sodium
Magnesium stearate
Opadry, acryl eze pink.

6.2 incompatibilities

Not applicable

6.3 shelf life

2 years

6.4 special precautions for storage

Store at temperature not exceeding 30°C, in dry place.
Keep out of reach of children.

6.5 Nature and contents of container

Carton box containing 1, 2 or 3 blisters (AL / AL) each of 10 enteric coated tablets and insert leaflet.

6.6 Instructions for use and handling and disposal:

Not applicable

7. MARKET AUTHORIZATION HOLDER

Eva Pharma for Pharmaceuticals & Medical Appliances, Giza, Egypt

8. MARKETING AUTHORISATION NUMBER(S)

05691/07783/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29-06-2017

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10. DATE OF REVISION OF THE TEXT

24-October-2023

11. REFERENCE