Front

# ESOMEPRAZOLE

## ESOFAG

40 mg Enteric-Coated Tablet
PROTON PUMP INHIBITOR

**PRODUCT NAME**
Esomeprazole

**NAME AND STRENGTH:**
Esomeprazole Tablets 40 mg

**PHARMACOLOGIC CATEGORY:**
Proton pump inhibitor

**PRODUCT DESCRIPTION:**
Pale Pink colored, circular, biconvex, enteric coated tablets plain on both surfaces.

**FORMULATION/COMPOSITION:**
Each enteric – coated tablet contains :
Esomeprazole Magnesium Trihydrate equivalent to Esomeprazole 40 mg

**PHARMACODYNAMICS/PHARMACOKINETICS:**
***Pharmacodynamics:***
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.
***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.

***Pharmacokinetics:***
***Absorption:*** Esomeprazole is acid labile and is administered orally as enteric-coated granules. *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.
Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.
***Distribution:*** 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.
***Biotransformation:*** Esomeprazole is completely metabolized 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.
***Elimination:*** The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolizers. 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. 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.

**INDICATIONS:**
Esomeprazole tablets are indicated in adults for: Gastro esophageal Reflux Disease (GERD)
Treatment of erosive reflux esophagitis; long-term management of patients with healed esophagitis to prevent relapse; symptomatic treatment of gastro esophageal reflux disease (GERD). In combination with appropriate antibacterial therapeutic regimens 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.
*Patients requiring continued NSAID therapy:* Healing of gastric ulcers associated with NSAID therapy; Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
*Treatment of Zollinger Ellison Syndrome:* Esomeprazole tablets are indicated in adolescents from the age of 12 years for: *Gastro esophageal Reflux Disease (GERD).* Treatment of erosive reflux esophagitis; long-term management of patients with healed esophagitis to prevent relapse; symptomatic treatment of gastro esophageal reflux disease (GERD)
In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*

**DOSAGE AND MODEL ROUTE OF ADMINISTRATION:**
***Adults:*** *Gastro esophageal 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 gastro esophageal 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. 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.

*In combination with appropriate antibacterial therapeutic regimens 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.
*Special Populations*
*Patients with 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.
*Patients with 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.
*Older people*
Dose adjustment is not required in the elderly.
Paediatric population
***Method of administration***
The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed. For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.
For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested.

**CONTRAINDICATIONS & PRECAUTION(S), WARNING(S):**
Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients,
Esomeprazole should not be used concomitantly with nelfinavir

**PRECAUTIONS & WARNINGS:**
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Esomeprazole Tablet may alleviate symptoms and delay diagnosis.
Long term use
Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
On demand treatment
Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.
***Helicobacter pylori* eradication:** When prescribing esomeprazole for eradication of *Helicobacter pylori*, possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolized via CYP3A4 such as cisapride.
**Gastrointestinal infections:** Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.
***Absorption of vitamin B12:*** Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.
***Hypomagnesaemia:*** Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
Risk of fracture
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognized risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
Combination with other medicinal products
Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.
Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole.
The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.
When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.
Sub acute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Esomeprazole Gastro-resistant Tablets. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

**PREGNANCY AND LACTATION:**
***Pregnancy:*** Clinical data on exposed pregnancies with Esomeprazole are insufficient. With the neither racemic mixture omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor fetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal 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.
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
***Lactation:*** It is not known whether esomeprazole is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.
***Fertility:*** Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

**INTERACTIONS:**
Effects of esomeprazole on the pharmacokinetics of other drugs

Size: 210 x 240 mm

*Protease inhibitors*
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.
For Atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. 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. The co-administration of omeprazole (20 mg qd) with Atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the Atazanavir exposure as compared with the exposure observed with Atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, $C_{max}$ and $C_{min}$ by 36–39 % and mean AUC, $C_{max}$ and $C_{min}$ for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar Pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and Atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.
*Methotrexate*: When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.
*Tacrolimus*: Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.
*Medicinal products metabolized by CYP2C19*: Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolizing enzyme. Thus, when esomeprazole is combined with drugs metabolized 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.
*Diazepam*: Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.
*Phenytoin*
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.
*Voriconazole*
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C and AUC by 15% and 41%, respectively.
*Cilostazol*
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.
*Cisapride*
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 ($_{t1/2}$) 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.
*Warfarin*
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.
*Clopidogrel*
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ Pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. Daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggression by an average of 14%.
When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups. Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.
*Investigated medicinal products with no clinically relevant interaction*
*Amoxicillin and quinidine*
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.
*Naproxen or rofecoxib*
Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.
**Effects of other medicinal products on the pharmacokinetics of esomeprazole**
*Medicinal products which inhibit CYP2C19 and/or CYP3A4*
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 CYP 3A4 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.
*Medicinal products which 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 esomeprazole serum levels by increasing the esomeprazole metabolism.
*Paediatric population*
Interaction studies have only been performing in adults.

**ADVERSE EFFECTS:**
Summary of the safety profile
Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.
*Tabulated list of adverse reactions*
The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to 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).

**Blood and lymphatic system disorders**
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia
**Immune system disorders**
Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
**Metabolism and nutrition disorders**
Uncommon: Peripheral oedema
Rare: Hyponatraemia
Not known: Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalemia
**Psychiatric disorders**
Uncommon: Insomnia
Rare: Agitation, confusion, depression
Very rare: Aggression, hallucinations
**Nervous system disorders**
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance
**Eye disorders**
Rare: Blurred vision
**Ear and labyrinth disorders**
Uncommon: Vertigo
**Respiratory, thoracic and mediastinal disorders**
Rare: Bronchospasm
**Gastrointestinal disorders**
Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis
Not known: Microscopic colitis
**Hepatobiliary disorders**
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease
**Skin and subcutaneous tissue disorders**
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known: Sub acute cutaneous lupus erythematosus
**Musculoskeletal and connective tissue disorders**
Uncommon: Fracture of the hip, wrist or spine
Rare: Arthralgia, myalgia
Very rare: Muscular weakness
**Renal and urinary disorders**
Very rare: Interstitial nephritis; in some patients renal failure has been reported concomitantly.
**Reproductive system and breast disorders**
Very rare: Gynaecomastia
**General disorders and administration site conditions**
Rare: Malaise, increased sweating

**OVERDOSAGE AND TREATMENT:**
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 utilized.

**STORAGE CONDITION:**
Store at temperatures not exceeding 30°C.

**DOSAGE FORMS AND PACKAGING AVAILABLE:**
Esomeprazole Tablets 40 mg are packed in Alu/Alu Blister Pack of 10's (Box of 30)

**INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):**
Not Applicable

**NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:**
**Marketing Authorization Holder**
Brown & Burk Philippines Inc.
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines

**NAME AND ADDRESS OF MANUFACTURER:**
**MICRO LABS LIMITED**
92, Sipcot Industrial Complex,
Hosur – 635 126, India.

**CAUTION STATEMENT:**
FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

**ADR REPORTING STATEMENT:**
"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sigh of Adverse Drug Reaction.

**REGISTRATION NUMBER:**
DR NO: XY40931

**DATE OF FIRST AUTHORIZATION:**
22 June 2012

**DATE OF REVISION OF PACKAGE INSERT:**
Feb. 2017