FASTESO®
(Esomeprazole)

فاسٹ ایسو

COMPOSITION:
FASTESO 20mg
Each Enteric-coated tablet contains:
Esomeprazole……20mg (as Esomeprazole magnesium trihydrate)
FASTESO 40mg
Each Enteric-coated tablet contains:
Esomeprazole……40mg (as Esomeprazole magnesium trihydrate)
(PharmEvo Specs.)

DESCRIPTION
FASTESO tablet contains Esomeprazole, which is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Esomeprazole magnesium trihydrate is chemically designated as bis(5-methoxy-2- [(S)- [(4 -methoxy-3,5 -dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. Its molecular formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$

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. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

Microbiology
Esomeprazole, amoxicillin, and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori (H. pylori)* in vitro and in clinical infections.

Pharmacokinetics

Absorption
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. The AUC after administration of a single 40 mg dose of Esomeprazole is decreased by 43% to 53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

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

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 Esomeprazole's metabolism is dependent upon the CYP 2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP 3A4 which forms the sulphone metabolite. Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

Excretion
The plasma elimination half-life of Esomeprazole is approximately 1 to 1.5 hours. Less than 1% of 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.

INDICATIONS

1. Treatment of Gastroesophageal Reflux Disease (GERD)
• **Healing of Erosive Esophagitis:** Esomeprazole is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis.
• **Maintenance of Healing of Erosive Esophagitis:** Esomeprazole is indicated to maintain symptom resolution and healing of erosive esophagitis.
• **Symptomatic Gastro esophageal Reflux Disease:** Esomeprazole is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD

2. Risk Reduction of NSAID-Associated Gastric Ulcer
Esomeprazole 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.
Esomeprazole is also indicated in the healing of gastric ulcers resulting from NSAID therapy

3. *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Esomeprazole, in combination with appropriate therapeutic antimicrobial regimen, 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.

4. Pathological Hyper secretory Conditions Including Zollinger-Ellison Syndrome
Esomeprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

Note: FASTESO (Esomeprazole) tablets can be used for adults and adolescents above 12 years of age

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily**
Symptomatic Gastro esophageal Reflux Disease	20 mg	Once Daily for 4 Weeks***
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months**
***H.pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**	20-40 mg	Once daily for 10-14 days $
Pathological Hyper secretory conditions including Zollinger-Ellison Syndrome	40 mg†	‡Twice Daily

*The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks of treatment may be considered.
**Not more than 6 months
***If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.
†The dosage of Esomeprazole in patients with pathological hyper secretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.
‡Doses up to 240 mg daily have been administered
$ Along with combination antimicrobial therapy

Note: If higher doses of Esomeprazole as in Zollinger Ellison syndrome are required for younger adolescents patients they should be administered with care upon physician's judgment as safety and efficacy with these high doses in hypersecretory conditions like Zollinger Ellison syndrome has not been established in adolescent patients 12-17 years of age.

Dosing considerations and dosing adjustment in Special Populations

Renal impairment
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.

Hepatic impairment
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.

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

CONTRAINDICATIONS
• Esomeprazole is contraindicated in patients with known hypersensitivity to esomeprazole or substituted benzimidazoles. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria

WARNINGS AND PRECAUTIONS

Concurrent gastric malignancy
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Esomeprazole may alleviate symptoms and delay diagnosis. Symptomatic response to therapy with Esomeprazole 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.

Acute Interstitial Nephritis
Acute interstitial nephritis has been observed in patients taking PPIs including Esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Esomeprazole if acute interstitial nephritis develops.

Cyanocobalamin (Vitamin B-12) Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by 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.

Gastrointestinal infections and *Clostridium difficile* associated diarrhea
Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile* in hospitalized patients.
Clostridium difficile associated diarrhea should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Interaction with Clopidogrel
Avoid concomitant use of Esomeprazole with clopidogrel. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as Esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg Esomeprazole reduces the pharmacological activity of clopidogrel.

Bone Fracture
According to researches, 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 established treatment guidelines with adequate intakes of calcium and Vitamin D

Hypomagnesaemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Concomitant use of Esomeprazole with St John's Wort or Rifampin
Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease Esomeprazole concentrations. Avoid concomitant use of Esomeprazole with St. John's Wort or rifampin.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop Esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Concomitant use of Esomeprazole with Methotrexate
Concomitant use of PPIs with methotrexate (primarily at high dose of methotrexate;

may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

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 Fasteso. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

***Helicobacter pylori* eradication**
When prescribing esomeprazole for eradication of *Helicobacter pylori*, possible drug interactions for all components in the regimen should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when it is used with esomeprazole in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Effects on ability to drive and use machines
Esomeprazole has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported. If affected, patients should not drive or use machines.

ADVERSE REACTIONS

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 edema
Rare: Hyponatremia
Not known: Hypomagnesaemia, severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders
Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggressions, hallucinations
Nervous system disorders
Common: headache
Uncommon: dizziness, paraestheisa, 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, diarrhea, 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.

DRUG INTERACTIONS

Interference with Antiretroviral Therapy
Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and the development of antiviral drug resistance.
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.

Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.

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 or switching to alternative therapy 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.

Drugs with pH dependent absorption
Gastric acid suppression during treatment with Esomeprazole and other PPIs might decrease or increase the absorption of drugs with a gastric pH dependent absorption. As with other drugs that decrease intragastric acidity, the absorption of drugs such as ketoconazole, itraconazole, atazanavir, iron salts, mycophenolate mofetil and erlotinib can decrease while the absorption of digoxin can increase during treatment with Esomeprazole.
Concomitant treatment with omeprazole (20 mg daily) and digoxin increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However, caution should be exercised when Esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.
The clinical relevance of reduced Mycophenolate exposure on organ rejection has not been established in transplant patients receiving Esomeprazole and Mycophenolate mofetil (MMF). Use Esomeprazole with caution in transplant patients receiving MMF

Drugs 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, cilostazol, voriconazole 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.

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 coumarin derivatives.

Clopidogrel
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of Fasteso with clopidogrel. When using Fasteso, consider use of alternative anti-platelet therapy.

Rifampin and St John's Wort
Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin and St John's Wort) may lead to decreased esomeprazole serum levels. Avoid concomitant use of St. John's Wort or rifampin with Esomeprazole.

Combination Therapy with Clarithromycin
Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions. Because of these drug interactions, clarithromycin is contraindicated for Co-administration with certain drugs. (See Clarithromycin prescribing information)

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Category C. There are no adequate and well-controlled studies with Esomeprazole in pregnant women. Esomeprazole is the S-isomer of omeprazole. Available epidemiologic data fail to demonstrate an increased risk of major congenital malformations or other adverse pregnancy outcomes with first trimester omeprazole use. 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. Caution should be exercised when prescribing to pregnant women and Esomeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers
Esomeprazole is likely present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. Caution should be exercised when Esomeprazole is administered to a nursing woman.

Elderly
No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment
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. No dosage adjustment is needed in patients with mild to moderate impairment. Due to limited experience in patients with severe renal insufficiency; such patients should be treated with caution.

Hepatic impairment
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 dosage 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 20 mg once daily should not be exceeded.

Pediatric Use:
FASTESO tablets are not recommended for patients less than 12 years of age.

OVERDOSAGE
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. Reports of overdosage with omeprazole in humans may also be relevant Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience.
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.

PRESENTATION
Fasteso 20mg Tablets : Pack of 14 Tablets.
Fasteso 40mg Tablets : Pack of 14 Tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.

ہدایات
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔

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Manufactured by:
PharmEvo (Pvt.) Ltd.
Plot # A-29, North Western Industrial Zone,
Port Qasim, Karachi-75020, Pakistan.
www.pharmevo.biz

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