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# Espra®

(Esomeprazole)

# ایسپرا

**COMPOSITION:**
***Espra Capsule 20 mg:***
Each capsule contains:
Esomeprazole Magnesium equivalent to
Esomeprazole ..... 20 mg.

**Product Specs.:** USP

***Espra Capsule 40 mg:***
Each capsule contains:
Esomeprazole Magnesium equivalent to
Esomeprazole ..... 40 mg.

**Product Specs.:**USP

**DESCRIPTION:**
The active ingredient in the proton pump inhibitor ESPRA is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2 pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its molecular formula is $(C_{17}H_{18}N_3O_3S)2Mg \times 3H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis.

**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.
**Pharmacokinetics:**
***Absorbtion:***
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 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 µmol•hr/L on Day 1 to 11.2 µmol•hr/L on Day 5 after 40 mg once daily dosing.
***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 CYP2C19 isoenzyme, the remaining amount is dependent on CYP3A4. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP 2C19 and are termed Poor metabolizers.
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.
***Elimination:***
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.
**Pharmacokinetics in Special Populations:**
***Hepatic Insufficiency:***
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.
***Renal Impairment:***
The pharmacokinetics of ESPRA 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.

**INDICATIONS AND USAGE:**
***Treatment of Gastroesophageal Reflux Disease (GERD):***
***Healing of Erosive Esophagitis:***
ESPRA 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 ESPRA may be considered. In infants 1 month to less than 1 year, ESPRA is indicated for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD.
***Maintenance of Healing of Erosive Esophagitis:***
ESPRA is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.
***Symptomatic Gastroesophageal Reflux Disease:***
ESPRA 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:***
ESPRA 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.
***H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence:***
Triple Therapy (ESPRA plus amoxicillin and clarithromycin): ESPRA, 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: is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

**DOSAGE AND ADMINISTRATION:**

| Indication | Dose | Frequency |
|---|---|---|
| **Gastroesophageal Reflux Disease (GRED)** | | |
| **Adults** | 20 mg or 40 mg | Once daily for 4-8 weeks |
| **12 - 17 years** | 20 mg or 40 mg | Once daily for 8 weeks |
| **1 - 11 years** | 10 mg or 20 mg | Once daily for 8 weeks |
| **1 months to less than 1 year.** | 2.5 mg, 5 mg or 10 mg (based on weight). | Once daily, up to 6 weeks for erosive esophagitis (EE) due due to acid-mediated GERD only. |
| **Risk Reduction of NSAID-Associated Gastric Ulcer** | 20 mg or 40 mg | Once daily for up to 6 months |
| **H. pylori Eradication (Triple Therapy):** | | |
| **ESPRA** | 40 mg | Once daily for 10 days |
| **Amoxicillin** | 1000 mg | Twice daily for 10 days |
| **Clarithromycin** | 50 mg | Twice daily for 10 days |
| **Pathological Hypersecretory Conditions** | 40 mg | Twice daily |

**CONTRAINDICATIONS:**
ESPRA is contraindicated in patients with known hypersensitivity to proton pump inhibitors.Hypersensitivity reactions, e.g., angioedema and anaphylactic shock, have been reported with ESPRA use.

**WARNINGS AND PRECAUTIONS:**
***Concurrent Gastric Malignancy:***
Symptomatic response to therapy with ESPRA 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.
***Cyanocobalamin deficiency:***
Daily treatment with acid suppressing agents may lead to cyancobalamin deficiency due to malabsorbtion.
***Cutaneous and systemic lupus erythematous:***
PPI use have been reported to be associated with SLE with sub-acute Cutaneous (SCLE) and Sub-acute systemic lupus erythematous (SSLE) being the most common types, occurring from infants to elderly population.
***Clostridium difficile associated diarrhea:***
PPI therapy like ESPRA may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve
***Interaction 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. When using ESPRA consider alternative anti-platelet therapy.

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***Bone Fracture:*** PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine, risk was increased in patients who receive high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer).
***Hypomagnesemia:***
Hypomagnesemia related serious adverse events include tetany, arrhythmias, and seizures.In most patients, treatment of hypomagnesemia 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 hypomagnesemia (e.g., diuretics), consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.
***Concomitant use of ESPRA with St John's Wort or Rifampin:***
Avoid concomitant use of ESPRA with St John's Wort, or rifampin.
***Interactions with Diagnostic Investigations for Neuroendocrine Tumors:***
Stop esomeprazole treatment 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 ESPRA with Methotrexate:***
Concomitant use of PPIs with 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.

**DRUG INTERACTIONS:**
Esomerprazole may interfere with drugs for which gastric pH affects bioavailability (e.g. ketoconazole, iron salts, erlotinib, digoxin and mycophenolate mofetil). Patients treated with Espra and digoxin may need to be monitored for digoxin toxicity.
Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.
Esomerprazole may reduce the plasma levels of atazanavir, nelfinavir, and saquinavir.
**Concomitant treatment with a combined inhibitor of CYP2C19 and CYP3A4**, such as voriconazole, may result in more than doubling of the esomeprazole exposure.
**May increase systemic exposure of cilostazol and an active metabolite.** Consider dose reduction
**Clopidogrel:** Esomerprazol decreases exposure to the active metabolite of clopidogrel.
***Tacrolimus and Methotrexate:*** Esomerprazole may increase serum levels of tacrolimus and methotrexate.

**USE IN SPECIFIC POPULATIONS:**
***Pregnancy:***
Esomerprazole is the s-isomer of omeprazole. Although in population-based during the first trimester of pregnancy to omeprazole there was no increased risk of congenital anomalies but this drug should be used during pregnancy only if clearly needed.
***Nursing Mothers:***
It is not known whether this drug is excreted in human milk.Because many drugs are excreted in human milk a decision should be made whether to discontinue nursing or to discontinue the drug.
***Pediatric Use:***
- The safety and effectiveness of ESPRA have been established in pediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of **GERD**.
- The safety and effectiveness of ESPRA have been established in pediatric patients 1 month to less than 1 year for short-term treatment (up to 6 weeks) **of erosive esophagitis due to acid-mediated GERD.** However, the safety and effectiveness of ESPRA have not been established in patients less than 1 month of age.
- *1 to 17 years of age:* Use of esomeprazole in pediatric and adolescent patients 1 to 17 years of age for short-term treatment (up to eight weeks) of **GERD** is supported by results from adequate and well-controlled studies.
- *Neonates 0 to 1 month of age:* The safety and effectiveness of esomeparzole in neonates have not been established.

***Geriatric Use:***
No overall differences in safety and efficacy 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.

**ADVERSE REACTIONS:**
Most common adverse reactions:
- Adults (≥18 years) (incidence > 1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth
- Pediatric (1 to 17 years) (incidence > 2%) are headache, diarrhea, abdominal pain, nausea, and somnolence
- Pediatric (1 month to less than 1 year) (incidence 1%) are abdominal pain, regurgitation, tachypnea, and increased ALT

**OVERDOSAGE:**
Sign and symptoms included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth. 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.

**INSTRUCTIONS:**
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

**PRESENTATION:**
**ESPRA Capsule 20 mg** : Pack of 2 x 7 capsules.
**ESPRA Capsule 40 mg** : Pack of 2 x 7 capsules.

**ہدایات:**
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

*FOR FURTHER INFORMATION PLEASE CONTACT.*

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