Esomeprazole delayed-release capsules

DESCRIPTION

Exonar® is supplied in delayed-release capsules. Each capsule contains 20 mg or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets.
Inactive ingredients: Disodium hydrogen ortho phosphate; Talc; Titanium dioxide; Sodium lauryl sulfate; Sugar; Hydroxypropylmethyl cellulose; Methacrylic acid copolymer; Diethyl phthalate; Polysorbate 80; Sodium hydroxide; Starch; Methyl paraben sodium and Propyl paraben sodium.

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease (GERD):
Healing of Erosive Esophagitis: Exonar® is indicated for 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 week course of Exonar® may be considered.
Maintenance of Healing of Erosive Esophagitis: Exonar® is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.
Symptomatic Gastroesophageal Reflux Disease: Exonar® is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children.

Risk Reduction of NSAID-Associated Gastric Ulcer:
Exonar® 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 (Exonar® plus amoxicillin and clarithromycin): Exonar®, 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:
Exonar® is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

DOSAGE AND ADMINISTRATION

Exonar® is supplied as delayed-release capsules for oral administration. The recommended dosages are outlined in the table below. Exonar® should be taken at least one hour before meals.

The duration of proton pump inhibitor administration should be based on available safety and efficacy data specific to the defined indication and dosing frequency, as described in the Prescribing Information and individual patient medical needs. Proton pump inhibitor treatment should only be initiated and continued if the benefits outweigh the risks of treatment.

Table 1: Recommended Dosage Schedule of Exonar®

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 Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks ***
Pediatric (GERD)		
12 to 17 Year Olds: Short-term Treatment of GERD	20 mg or 40 mg	Once Daily for up to 8 Weeks
1 to 11 Year Olds +: Short-term Treatment of Symptomatic GERD	10 mg	Once Daily for up to 8 Weeks
Healing of Erosive Esophagitis		
weight < 20 Kg	10 mg	Once Daily for 8 Weeks
weight > 20 Kg	10 mg or 20 mg	Once Daily for 8 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**		
Triple Therapy:		
- Exonar®	40 mg	Once Daily for 10 Days
- Amoxicillin	1000 mg	Twice Daily for 10 Days
- Clarithromycin	500 mg	Twice Daily for 10 Days
Pathological Hypersecretory 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.

** Controlled studies did not extend beyond six months.

*** If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

+ Doses over 1 mg/kg/day have not been studied.

• The dosage of Exonar® in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.

••-- Doses up to 240 mg daily have been administered (See DRUG INTERACTIONS).

Special Populations
Geriatric: No dosage adjustment is necessary.
Renal Insufficiency: No dosage adjustment is necessary.
Hepatic Insufficiency: In patients with mild to moderate liver impairment (Child Pugh Classes A and B), no dosage adjustment is necessary. For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of Exonar® should not be exceeded.

Administration Options
Directions for use specific to the route and available methods of administration for each of these dosage forms are presented below.

Table 2: Administration options (See text following table for additional instructions)

Type	Route	Options
Delayed-Release Capsule	Oral	Capsule can be swallowed whole or Capsule can be opened and mixed with apple sauce
Delayed-Release Capsule	Nasogastric Tube	Capsule can be opened and the intact pellets emptied into a syringe and delivered through the nasogastric tube.

Exonar® delayed-release capsules should be swallowed whole.
Alternatively, for patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the Exonar® delayed-release capsule can be opened and the pellets inside the capsule carefully emptied onto the apple sauce. The pellets should be mixed with the applesauce and then swallowed immediately. The apple sauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/apple sauce mixture should not be stored for future use.
For patients who have a nasogastric tube in place, Exonar® delayed-release capsules can be opened and the intact pellets emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering Exonar® through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for pellets remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the pellets, the nasogastric tube should be flushed with additional water.
Do not administer the pellets if they have dissolved or disintegrated.
The suspension must be used immediately after preparation.

DOSAGE FORMS AND STRENGTHS

Exonar® delayed-release capsules, 20 mg - size 4 opaque, hard gelatin capsules with light green body and dark green cap, imprinted “ALG” on one part and “E20” on the other.
Exonar® delayed-release capsules, 40 mg - size 3 opaque, hard gelatin capsules with powder blue body and light blue cap, imprinted “ALG” on one part and “E40” on the other.

CONTRAINDICATIONS
Exonar® is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles. Hypersensitivity reactions e.g., angioedema and anaphylactic reaction/shock have been reported with esomeprazole use.

WARNINGS AND PRECAUTIONS
Concurrent Gastric Malignancy: Symptomatic response to therapy with Exonar® 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): [See Warnings and Precautions in the prescribing information for amoxicillin for complete information.]
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.
Risks of Clarithromycin (as Part of H. pylori Triple Therapy): [See Warnings and Precautions in the prescribing information for clarithromycin for complete information.]
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.

ADVERSE REACTIONS
Clinical Trials Experience:
The safety of esomeprazole was evaluated in over 15000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8500 patients in the United States and over 6500 patients in Europe and Canada. Over 2900 patients were treated in long-term studies for up to 6 -12 months. In general, esomeprazole was well tolerated in both short and long-term clinical trials.
The safety of esomeprazole was evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD. In 109 pediatric patients aged 1 to 11 years, the most

frequently reported (at least 1%) treatment- related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17 years the most frequently reported (at least 2%) treatment-related adverse reactions in these patients were headache (8.1%), abdominal pain (2.7%), diarrhea (2%) and nausea (2%). No new safety concerns were identified in pediatric patients.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1240 patients on esomeprazole 20 mg, 2434 patients on esomeprazole 40 mg and 3008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions (≥ 1%) in all three groups were headache (5.5, 5.0 and 3.8 respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation and dry mouth occurred at similar rates among patients taking esomeprazole or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to esomeprazole with an incidence < 1% are listed below by body system:

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 lymphoadenopathy, 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.

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole, were reported in ≤ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone. Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium and thyroxine.
Endoscopic findings that were reported as adverse reactions include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus and mucosal discoloration.

Combination Treatment with Amoxicillin and Clarithromycin
In clinical trials using combination therapy with esomeprazole plus amoxicillin and clarithromycin, no additional adverse reactions specific to these drug combinations were observed. Adverse reactions that occurred were limited to those observed when using esomeprazole, amoxicillin or clarithromycin alone.
The most frequently reported drug-related adverse reactions for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%) and abdominal pain (3.7%). No treatment-emergent adverse reactions were observed at higher rates with triple therapy than were observed with esomeprazole alone.
In clinical trials using combination therapy with esomeprazole plus amoxicillin and clarithromycin, no additional increased laboratory abnormalities particular to these drug combinations were observed.
For more information on adverse reactions or laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions section.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of esomeprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:
Blood and Lymphatic: agranulocytosis, pancytopenia;
Eye: blurred vision;
Gastrointestinal: pancreatitis, stomatitis;
Hepatobiliary: hepatic failure, hepatitis with or without jaundice;
Immune System: anaphylactic reaction/shock;
Infections and Infestations: GI candidiasis;
Musculoskeletal and Connective Tissue: muscular weakness, myalgia;
Nervous System: hepatic encephalopathy, taste disturbance;
Psychiatric: aggression, agitation, depression, hallucination;
Renal and Urinary: interstitial nephritis;

Reproductive System and Breast: gynecomastia;
Respiratory, Thoracic and Mediastinal: bronchospasm;
Skin and Subcutaneous Tissue: alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

DRUG INTERACTIONS
Interference with Antiretroviral Therapy: Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. 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.
There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Drugs for Which Gastric pH Can Affect Bioavailability: Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, atazanavir, iron salts and digoxin).

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways: Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP 3A4. In vitro and in vivo studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin.
However, post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.
Esomeprazole may potentially interfere with CYP 2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and diazepam, a CYP 2C19 substrate, resulted in a 45% decrease in clearance of diazepam.
Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP 3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered.

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 cisapride, pimozide, astemizole, terfenadine, ergotamine or dihydroergotamine is contraindicated

SPECIFIC POPULATIONS

Pregnancy

FDA pregnancy category B

Reproductive studies in rats and rabbits with esomeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are, however, no adequate and well controlled studies of esomeprazole use in pregnancy. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Reproductive studies with esomeprazole have been performed in rats at doses up to 57 times the human dose and in rabbits at doses up to 35 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus.

Reproductive studies conducted with omeprazole on rats at oral doses up to 56 times the human dose and in rabbits at doses up to 56 times the human dose did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy loss. In rats treated with omeprazole at doses about 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. However, the excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for esomeprazole in rat carcinogenicity studies, 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.

Pediatric

The safety and effectiveness of esomeprazole have been established in pediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD. However, effectiveness has not been demonstrated in patients less than 1 year 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: extrapolation of results, already included in--- the currently approved labeling, from adequate and well-controlled studies that supported the approval of esomeprazole for adults and safety and pharmacokinetic studies performed in pediatric and adolescent patients. The safety and effectiveness of esomeprazole for other pediatric uses have not been established.

Neonates to less than one year of age: Because esomeprazole was not shown to be effective in the randomized, placebo-controlled study for this age group, the use of esomeprazole in patients less than 1 year is not indicated.

Geriatric

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.

OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia and intermittent clonic convulsions.

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). 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 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.

HOW SUPPLIED/STORAGE AND HANDLING

Exonar®---- delayed-release capsules, 20 mg and 40 mg are available each in blister packs of 14 capsules.

Store in a dry place below 25°C, protected from light. Do not refrigerate.

PATIENT COUNSELING INFORMATION

• Patients should inform their physicians if they are taking, or begin taking, other medications, because Exonar® can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [see Drug Interactions].
• Patients should know that antacids may be used while taking Exonar®.
• Patients should be advised to take Exonar® at least one hour before a meal.
• Patients who are prescribed Exonar® delayed-release capsules, should be advised not to chew or crush the capsules.
• Patients should be advised if they open Exonar® delayed-release capsules to mix the pellets with food, the pellets should only be mixed with apple sauce. Use with other foods has not been evaluated and is not recommended.
• Patients who are advised to open the Exonar® delayed-release capsules before taking them, should be instructed in the proper technique for administration [see Dosage and Administration].

This is a medicament

-A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

-The doctor and the pharmacist are experts in medicine, its benefits and risks.
-Do not by yourself interrupt the period of treatment prescribed.
-Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children.

Do not use after expiry date.

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