



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES safely and effectively. See full prescribing information for ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES.

ESOMEPRAZOLE magnesium delayed-release capsules, USP for oral use
Initial U.S. Approval: 1989 (omeprazole)

RECENT MAJOR CHANGES

Warnings and Precautions, Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.10)	03/2014
Contraindications (4)	12/2014
Warnings and Precautions, Acute Interstitial Nephritis (5.3)	12/2014
Warnings and Precautions, Cyanocobalamin (vitamin B-12) Deficiency (5.4)	12/2014

INDICATIONS AND USAGE

Esomeprazole magnesium delayed-release capsule, USP is a proton pump inhibitor indicated for the following:

- Treatment of gastroesophageal reflux disease (GERD) (1.1)
- Risk reduction of NSAID-associated gastric ulcer (1.2)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4)

DOSE AND ADMINISTRATION

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)	Adults	20 mg or 40 mg
	12 to 17 years	Once daily for 4 to 8 weeks
	1 to 11 years	Once daily for up to 8 weeks
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once daily for up to 6 months
	40 mg	Twice daily

See full prescribing information for administration options (2). Patients with severe liver impairment do not exceed dose of 20 mg (2).

DOSE FORMS AND STRENGTHS

- Esomeprazole magnesium delayed-release capsules: 20 mg and 40 mg (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred) (4)

WARNINGS AND PRECAUTIONS

- Symptomatic response does not preclude the presence of gastric malignancy (5.1)
- Atrophic gastritis has been noted with long-term omeprazole use (5.2)

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- 7.1 Interference with Antiretroviral Therapy
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- 1.1 Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

Esomeprazole magnesium delayed-release capsules, USP are 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 week course of esomeprazole magnesium delayed-release capsules, USP may be considered.

Maintenance of Healing of Erosive Esophagitis

Esomeprazole magnesium delayed-release capsules, USP are indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

Esomeprazole magnesium delayed-release capsules, USP are 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.

2 DOSAGE AND ADMINISTRATION

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.

3 DOSAGE FORMS AND STRENGTHS

Esomeprazole magnesium delayed-release capsules, 40 mg are blue opaque colored size "3" hard gelatin capsules imprinted with "H" on cap and "72" on body filled with pale yellow colored pellets.

4 CONTRAINDICATIONS

Esomeprazole magnesium delayed-release capsules, 40 mg are blue opaque colored size "3" hard gelatin capsules imprinted with "H" on cap and "71" on body filled with pale yellow colored pellets.

5 WARNINGS AND PRECAUTIONS

Esomeprazole magnesium delayed-release capsules are contraindicated in patients with known hypersensitivity to substituted benzimidazole (vitamin B-12) capsules or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticarial (see **Adverse Reactions** (6)).

6 ADVERSE REACTIONS

Symptomatic response to therapy with esomeprazole magnesium delayed-release capsules does not preclude the presence of gastric malignancy.

7 DRUG INTERACTIONS

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

8 ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole magnesium delayed-release capsules. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiosyncratic hypersensitivity reaction. Discontinue esomeprazole magnesium delayed-release capsules if acute interstitial nephritis develops (see **Contraindications** (4)).

9 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) due to hypochlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered in patients with clinical symptoms consistent with cyanocobalamin deficiency are observed.

10 CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHEA

Published observational studies suggest that PPI therapy like esomeprazole magnesium delayed-release capsules may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered in patients with diarrhea that is generally attributed to an idiosyncratic hypersensitivity reaction. Discontinue esomeprazole magnesium delayed-release capsules if the condition being treated.

11 CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHEA (CDAD)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents.

12 INTERACTION WITH CLOPIDOGREL

Avoid concomitant use of esomeprazole magnesium delayed-release capsules with clopidogrel. Clopidogrel is a prodrug, and its activation to a platelet aggregation inhibitor is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibits CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When administering esomeprazole magnesium delayed-release capsules consider alternative anti-platelet therapy (see **Drug Interactions** (7.3) and **Pharmacokinetics** (12.3)).

13 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 established treatment guidelines (see **Dosage and Administration** (2) and **Adverse Reactions** (6.2)).

14 HYPOMAGNEMISIA

Hypomagnesemia, 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 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), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (see **Adverse Reactions** (6.2)).

15 CONCOMITANT USE OF ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES 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 (see **Drug Interactions** (7.3)). Avoid concomitant use of esomeprazole magnesium delayed-release capsules with St. John's Wort, or rifampin.

16 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 may vary (see **Clinical Pharmacology** (12.2)).

- Acute interstitial nephritis has been observed in patients taking PPIs. (5.3)
- Cyanocobalamin (vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) of proton pump inhibitor (PPI) may lead to malabsorption of cyanocobalamin (vitamin B-12) due to hypochlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered in patients with clinical symptoms consistent with cyanocobalamin deficiency are observed. (5.4)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.5)
- Avoid concomitant use of esomeprazole magnesium delayed-release capsules with clopidogrel. (5.6)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.7)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs. (5.8)
- Avoid concomitant use of esomeprazole magnesium delayed-release capsules with St. John's Wort or rifampin due to the potential reduction in esomeprazole levels. (5.9, 7.3)
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.10, 12.2)

ADVERSE REACTIONS

Most common adverse reactions (6.1):

- 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

DRUG INTERACTIONS

May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended; if saquinavir is used with esomeprazole magnesium delayed-release capsules, monitor for toxicity and adjust dosing as needed. (7.1)

May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, digoxin and mycophenolate mofetil). Patients treated with esomeprazole magnesium delayed-release capsules and digoxin may need to be monitored for digoxin toxicity. (7.2)

CONCOMITANT USE OF ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES WITH ST. JOHN'S WORT OR RIFAMPIN

Drugs which induce CYP2C19 and 3A4 may raise esomeprazole levels. (7.3)

Clopidogrel: esomeprazole magnesium delayed-release capsule decreases exposure to the active metabolite of clopidogrel. (7.3)

May increase systemic exposure of clostazolol and an active metabolite. Consider dose reduction. (7.4)

WARNINGS AND PRECAUTIONS

Tacrolimus: Esomeprazole magnesium delayed-release capsules may increase serum levels of tacrolimus (7.5)

Methotrexate: esomeprazole magnesium delayed-release capsules may increase serum levels of methotrexate. (7.7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

PATIENT COUNSELING INFORMATION AND FDA-Approved Medication Guide.

Revised : 10/2015

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- 7.4 Interactions with Investigations of Neuroendocrine Tumors
- 7.5 Tacrolimus
- 7.6 Methotrexate

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- *Sections or subsections omitted from the full prescribing information are not listed.

Esomeprazole Magnesium Delayed-Release Capsules

Esomeprazole magnesium delayed-release capsules should be swallowed whole. Alternatively, for patients who have difficulty swallowing capsules, one tablet of esomeprazole magnesium delayed-release capsules can be added to an empty bowl and the esomeprazole magnesium delayed-release capsule can be opened, and the granules inside the capsule carefully emptied onto the applesauce. The granules should be mixed with the applesauce and then swallowed immediately, do not store for future use. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The granules should not be chewed or crushed. If the granules/applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

For patients who have a nasogastric tube in place, esomeprazole magnesium delayed-release capsules can be opened and the intact granules 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 esomeprazole magnesium delayed-release capsules 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 granules 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 granules, the nasogastric tube should be flushed with additional water. Do not administer the granules if they have dissolved or disintegrated.

The mixture must be used immediately after preparation.

3 DOSAGE FORMS AND STRENGTHS

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6 ADVERSE REACTIONS

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

7 DRUG INTERACTIONS

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

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Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole magnesium delayed-release capsules. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiosyncratic hypersensitivity reaction. Discontinue esomeprazole magnesium delayed-release capsules if acute interstitial nephritis develops (see **Contraindications** (4)).

9 CYANOCOBALAMIN (VITAMIN B-12) DEFICIENCY

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14 HYPOMAGNEMISIA

Hypomagnesemia, 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 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), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (see **Adverse Reactions** (6.2)).

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- 5.11 Concomitant use of Esomeprazole Magnesium Delayed-Release Capsules with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) 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 (see **Drug Interactions** (7.7)).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The safety of esomeprazole magnesium delayed-release capsules were evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term clinical trials up to 12 months. In general, esomeprazole magnesium delayed-release capsules were well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on esomeprazole magnesium delayed-release capsules 20 mg, 2,434 patients on esomeprazole magnesium delayed-release capsules 40 mg, and 3,008 patients on esomeprazole 20 mg daily. The most frequently occurring adverse reactions (>1%) in all three groups were headache (5.5, 5, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, constipation, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole magnesium delayed-release capsules or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to esomeprazole magnesium delayed-release capsules 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 flashes, fatigue, fever, flu-like syndrome, 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, melaena, stool disorder, pharynx disorder, serous gastritis, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting.

Hearing: earache, tinnitus.

Hematologic: anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.

Head: binocularismus, hepatic function abnormal, SGOT increased, SGPT increased.

Metabolic/Nutritional: glycosuria, hyperuricemia, hypotonia, 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, hyperosteoarthritis, insomnia, potassium migraine, potassium migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.

Respiratory: dysmenorrhea, menstrual disorder, vaginitis.

Skin and Appendages: acne, acne nodular, 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, monilia, genital monilia, polyuria.

Visual: conjunctivitis, vision abnormal.

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole magnesium delayed-release capsules, 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 (see **Clinical Pharmacology** (12)). 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.

The incidence of treatment-related adverse reactions during 6-month maintenance treatment was similar to placebo. The incidence of adverse reactions including dyspepsia was seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse reactions that were reported as possibly or probably related to esomeprazole magnesium delayed-release capsules were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Pediatrics

The safety of esomeprazole magnesium delayed-release capsules were evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD (see **Contraindications** (4)). In total, 264 pediatric patients aged 1 to 11 years, and the most frequently reported (> 1%) treatment-related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.5%). In 149 pediatric patients aged 12 to 17 years, the most frequently reported (> 1%) 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole magnesium delayed-release capsules. 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; microscopic colitis



Manufactured by:
HETERO LABS LIMITED
 22-110, I.D.A. Jeedimetla,
 Hyderabad-500055, India.
 Revised: October 2015

12 CLINICAL PHARMACOLOGY

12.1 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 esomeprazole 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.

12.2 Pharmacodynamics

Antisecretory Activity

The effect of esomeprazole magnesium delayed-release capsules on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, esomeprazole magnesium delayed-release capsules 40 mg and 20 mg capsules were administered over 5 days. The results are shown in the Table 3.

Table 3: Effect on Intragastric pH on Day 5 (N=36)

Parameter	Esomeprazole magnesium delayed-release capsules 40 mg	Esomeprazole magnesium delayed-release capsules 20 mg
% Time Gastric pH >4 (Hours)	70%*	53% (16.8 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9*	4.1
Coefficient of variation	16%	27%

* Gastric pH was measured over a 24-hour period
 † p < 0.01 Esomeprazole magnesium delayed-release capsules 40 mg vs. Esomeprazole magnesium delayed-release capsules 20 mg

In a second study, the effect on intragastric pH of esomeprazole magnesium delayed-release capsules 40 mg administered once daily over a five day period was similar to the first study, (% time with pH > 4 was 68% or 16.3 hours).

Serum Gastrin Effects

The effect of esomeprazole magnesium delayed-release capsules on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6 to 12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. The increased CgA levels 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.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies of esomeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoma tumors and ECL cell hyperplasia was observed in both male and female animals [see *Nonclinical Toxicology* (13.1)]. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H₂-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients (both children and adults) treated with esomeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with esomeprazole magnesium delayed-release capsules (10, 20 or 40 mg/day) up to 6 to 12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

Esomeprazole magnesium delayed-release capsules had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of esomeprazole magnesium delayed-release capsules on the endocrine system were assessed using esomeprazole studies. Esomeprazole given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecalciferol, or secretin.

12.3 Pharmacokinetics

Absorption

Esomeprazole magnesium delayed-release capsules contain a bioequivalent enteric-coated granule formulation of esomeprazole magnesium. Bioequivalency is based on a single dose (40 mg p.o. once daily) in 94 healthy male and female volunteers under fasting conditions. 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 4.52 µmol·h/L on Day 1 to 11.2 µmol·h/L on Day 5 after 40 mg once daily dosing. The AUC after administration of a single 40 mg dose of esomeprazole magnesium delayed-release capsules is decreased by 43% to 53% after food intake compared to fasting conditions. Esomeprazole magnesium delayed-release capsules should be taken at least one hour before meals.

The pharmacokinetic profile of esomeprazole magnesium delayed-release capsules were determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once-daily administration of 20 mg and 40 mg capsules of esomeprazole magnesium over a period of five days. The results are shown in the Table 4.

Table 4: Pharmacokinetic Parameters of Esomeprazole Magnesium Delayed-Release Capsules on Day 5 Following Oral Dosing for 5 Days

Parameter* (CV)	Esomeprazole Magnesium Delayed-Release Capsules 40 mg	Esomeprazole Magnesium Delayed-Release Capsules 20 mg
AUC (µmol·h/L)	12.6 (42%)	4.2 (59%)
C _{max} (µmol/L)	4.7 (37%)	2.1 (45%)
T _{max} (h)	1.6	1.6
t _{1/2} (h)	1.5	1.2

*Values represent the geometric mean, except the T_{max}, which is the arithmetic mean. CV = Coefficient of variation

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 44% is dependent on CYP 3A4 which forms the sulfone metabolite. CYP 2C19 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. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

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.

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.

Concomitant Use with Clopidogrel

Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacokinetic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

Concomitant Use with Myphenolate Mofetil

Administration of esomeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of esomeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the C_{max} and 23% reduction in the AUC of MMF.

Special Populations

Geriatric

The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric

1 to 11 Years of Age

The pharmacokinetics of esomeprazole were studied in pediatric patients with GERD aged 1 to 11 years. Following once daily dosing for 5 days, the total exposure (AUC) for the 10 mg dose in patients aged 6 to 11 years was similar to that seen with the 20 mg dose in adults and adolescents aged 12 to 17 years. The total exposure for the 10 mg dose in patients aged 1 to 5 years was approximately 30% higher than the 10 mg dose in patients aged 6 to 11 years. The total exposure for the 20 mg dose in patients aged 6 to 11 years was higher than that observed with the 20 mg dose in 12 to 17-year-olds and adults, but lower than that observed with the 40 mg dose in 12 to 17-year-olds and adults. See Table 5.

Table 5: Summary of PK Parameters in 1 to 11 Year Olds with GERD following 5 Days Of Once-Daily Oral Esomeprazole Treatment

Parameter	1 to 5 Year Olds		6 to 11 Year Olds	
	10 mg (N=8)	10 mg (N=7)	20 mg (N=6)	20 mg (N=6)
AUC (µmol·h/L)*	4.83	3.70	6.28	6.28
C _{max} (µmol/L)	2.98	1.77	3.73	3.73
t _{max} (h)†	1.44	1.79	1.75	1.75
t _{1/2} (h)*	0.74	0.88	0.73	0.73
Cl/F (L/h)*	5.99	7.84	9.22	9.22

*Geometric mean; †arithmetic mean

12 to 17 Years of Age

The pharmacokinetics of esomeprazole magnesium delayed-release capsules were studied in 28 adolescent patients with GERD aged 12 to 17 years inclusive, in a single center study. Patients were randomized to receive esomeprazole magnesium delayed-release capsules 20 mg or 40 mg once daily for 5 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age, and more than dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, esomeprazole magnesium delayed-release capsules pharmacokinetics in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. See Table 6.

Table 6: Comparison of PK Parameters in 12 to 17 Year Olds with GERD and Adults with Symptomatic GERD Following the Repeated Daily Oral Dose Administration of Esomeprazole*

Parameter	12 to 17 Year Olds (N=28)		Adults (N=36)	
	20 mg	40 mg	20 mg	40 mg
AUC (µmol·h/L)	3.65	13.86	4.2	12.6
C _{max} (µmol/L)	1.45	5.13	2.1	4.7
t _{max} (h)	2	1.75	1.6	1.6
t _{1/2} (h)	0.82	1.22	1.2	1.5

Data presented are geometric means for AUC, C_{max} and t_{1/2}, and median value for t_{max}.

*Duration of treatment for 12 to 17 year olds and adults were 8 days and 5 days, respectively. Data were obtained from two independent studies.

Gender

The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

The steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. 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 [see *Dosage and Administration* (2)].

Renal Insufficiency

The pharmacokinetics of esomeprazole magnesium delayed-release capsules 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.

Other pharmacokinetic observations

Co-administration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole. Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole magnesium delayed-release capsules were assessed using studies of esomeprazole, of which esomeprazole is an enantiomer. In two 24-month oral carcinogenicity studies in rats, esomeprazole at daily doses of 1.7, 3.4, 13.8, 44, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of esomeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg esomeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs. 10% controls). By the second year, the incidence of ECL cell hyperplasia was similar in both smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of esomeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow clastogenic aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Esomeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, in *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using esomeprazole studies. Esomeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

13.2 Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 4.2 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole [see *Pregnancy, Animal Data* (8.1)].

Juvenile Animal Study

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium delayed-release capsules at doses of 70 to 280 mg/kg/day (about 1.7 to 68 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium delayed-release capsules from postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 3.4 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

14.1 Healing of Erosive Esophagitis

The healing rates of esomeprazole magnesium delayed-release capsules 40 mg, esomeprazole magnesium delayed-release capsules 20 mg, and omeprazole 20 mg (the approved dose for this indication) were evaluated in patients with endoscopically diagnosed erosive esophagitis in four multicenter, double-blind, randomized studies. The healing rates at Weeks 4 and 8 were evaluated and are shown in the Table 7.

Table 7: Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level*
1	588	Esomeprazole magnesium delayed-release capsules 20 mg	68.7%	90.6%	N.S.
		Omeprazole 20 mg	69.5%	88.3%	
2	654	Esomeprazole magnesium delayed-release capsules 40 mg	75.9%	94.1%	p < 0.001
		Esomeprazole magnesium delayed-release capsules 20 mg	70.5%	89.9%	
3	576	Esomeprazole magnesium delayed-release capsules 40 mg	71.5%	92.2%	N.S.
		Omeprazole 20 mg	64.7%	86.9%	
4	1216	Esomeprazole magnesium delayed-release capsules 40 mg	68.6%	89.8%	p < 0.001
		Omeprazole 20 mg	81.7%	93.7%	
	1209	Omeprazole 20 mg	68.7%	84.2%	

*log-rank test vs. omeprazole 20 mg
 N.S. = not significant (p > 0.05).

In these studies, patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in the Table 8.

Table 8: Sustained Resolution† of Heartburn (Erosive Esophagitis Patients)

Study	No. of Patients	Treatment Groups	Cumulative Percent† with Sustained Resolution		Significance Level*
			Day 14	Day 28	
1	573	Esomeprazole magnesium delayed-release capsules 20 mg	64.3%	72.7%	N.S.
		Omeprazole 20 mg	64.1%	70.9%	
2	655	Esomeprazole magnesium delayed-release capsules 40 mg	68.1%	74.2%	p < 0.001
		Esomeprazole magnesium delayed-release capsules 20 mg	62.9%	70.1%	
3	626	Esomeprazole magnesium delayed-release capsules 20 mg	56.5%	66.6%	N.S.
		Omeprazole 20 mg	65.4%	73.9%	
4	568	Esomeprazole magnesium delayed-release capsules 40 mg	65.5%	73.1%	N.S.
		Omeprazole 20 mg	65.5%	73.1%	
4	1187	Esomeprazole magnesium delayed-release capsules 40 mg	67.6%	75.1%	p < 0.001
		Omeprazole 20 mg	62.5%	70.8%	

*Defined as 7 consecutive days with no heartburn reported in daily patient diary.

†Defined as the cumulative proportion of patients who have reached the state of sustained resolution.

*log-rank test vs. omeprazole 20 mg
 N.S. = not significant (p > 0.05).

In these four studies, the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 3 days for esomeprazole magnesium delayed-release capsules 40 mg, 7 to 8 days for esomeprazole magnesium delayed-release capsules 20 mg and 7 to 9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of esomeprazole magnesium delayed-release capsules with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

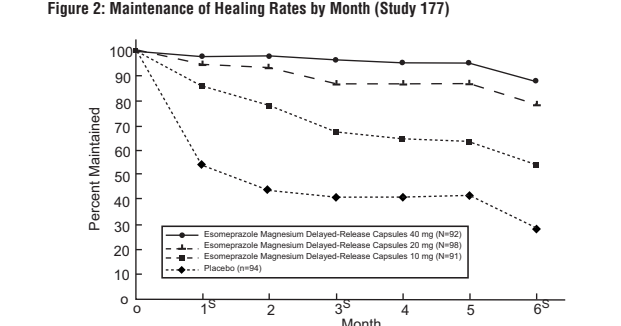
Long-Term Maintenance of Healing of Erosive Esophagitis

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate esomeprazole magnesium delayed-release capsules 40 mg (N=174), 20 mg (N=180), 10 mg (N=168) or placebo (N=171) once daily over six months of treatment.

No additional clinical benefit was seen with esomeprazole magnesium delayed-release capsules 40 mg over esomeprazole magnesium delayed-release capsules 20 mg.

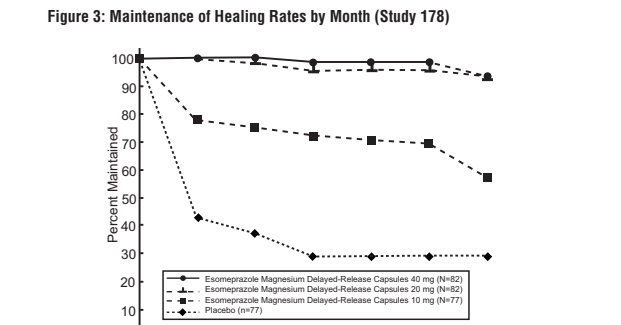
The percentages of patients that maintained healing of erosive esophagitis at the various time points are shown in the Figures 2 and 3.

Figure 2: Maintenance of Healing Rates by Month (Study 177)



§ = scheduled visit

Figure 3: Maintenance of Healing Rates by Month (Study 178)



§ = scheduled visit

§ = scheduled visit

Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with esomeprazole magnesium delayed-release capsules compared to placebo.

In both studies, the proportion of patients on esomeprazole magnesium delayed-release capsules who remained in remission and were free of heartburn and other GERD symptoms was well-differentiated from placebo.

In a third multicenter open label study of 808 patients treated for 12 months with esomeprazole magnesium delayed-release capsules 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for six months and 89.4% for one year.

14.2 Symptomatic Gastroesophageal Reflux Disease (GERD)

Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 717 patients comparing four weeks of treatment with esomeprazole magnesium delayed-release capsules, 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had a 6-month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients that were symptom-free of heartburn was significantly higher in the esomeprazole magnesium delayed-release capsules groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

No additional clinical benefit was seen with esomeprazole magnesium delayed-release capsules 40 mg over esomeprazole magnesium delayed-release capsules 20 mg.

The percent of patients symptom-free of heartburn by day are shown in the Figures 4 and 5.

Figure 4: Percent of Patients Symptom-Free of Heartburn by Day (Study 225)

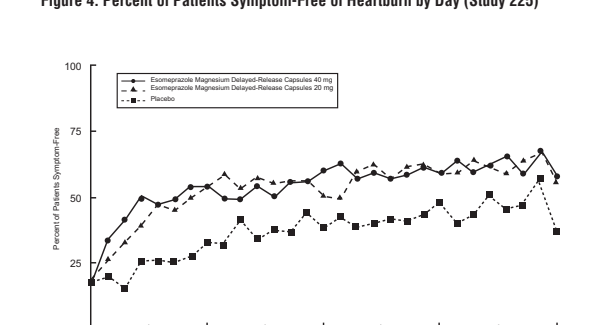
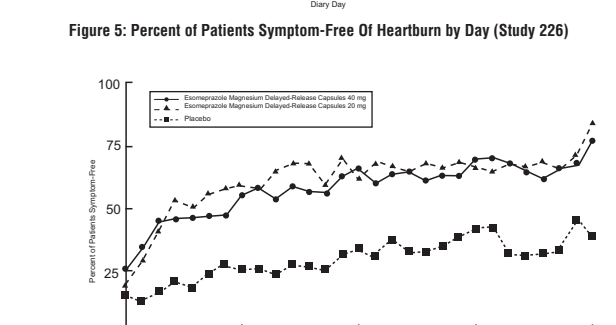


Figure 5: Percent of Patients Symptom-Free of Heartburn by Day (Study 226)



In three European symptomatic GERD trials, esomeprazole magnesium delayed-release capsules 20 mg and 40