ESOMEPRAZOLE STRONTIUM- esomeprazole strontium capsule, delayed release
Amneal Pharmaceuticals LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ESOMEPRAZOLE STRONTIUM safely and effectively. See full prescribing information for ESOMEPRAZOLE STRONTIUM.

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

INDICATIONS AND USAGE

Esomeprazole strontium is a proton pump inhibitor indicated for adults for:

- Treatment of gastroesophageal reflux disease (GERD) (1.1)
- Risk reduction of NSAID-associated gastric ulcer (1.2)
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4)

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Adults	24.65 or 49.3 mg	Once daily for 4-8 weeks
Risk Reduction of NSAID-Associated Gastric Ulcer		
Adults	24.65 or 49.3 mg	Once daily for up to 6 months
***H. pylori* Eradication (Triple Therapy) in Adults:**		
Esomeprazole strontium	49.3 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		
Adults	49.3 mg	Twice daily

- See full prescribing information for full dosage and administration (2)
- Patients with severe liver impairment: do not exceed dose of 24.65 mg (2)

DOSAGE FORMS AND STRENGTHS

Delayed-Release Capsules (3):

- 24.65 mg of esomeprazole strontium (equivalent to 20 mg of esomeprazole)
- 49.3 mg of esomeprazole strontium (equivalent to 40 mg of esomeprazole)

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 therapy (5.2)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.3)
- Avoid concomitant use of esomeprazole strontium with clopidogrel. (5.4)
- 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. (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6)
- Avoid concomitant use of esomeprazole strontium with St. John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.7, 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. (5.8, 12.2)

ADVERSE REACTIONS

Most common adverse reactions in adults (≥18 years) (incidence ≥1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1‑877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Antiretroviral Drugs:* Use with atazanavir and nelfinavir is not recommended; if saquinavir is used with esomeprazole strontium, monitor for toxicity and consider saquinavir dose reduction (7.1)
- May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib and digoxin). May need monitoring for digoxin toxicity (7.2)
- *Combined Inhibitor of CYP 2C19 and 3A4:* May raise esomeprazole levels (7.3)
- *Clopidogrel:* Esomeprazole strontium decreases exposure to the active metabolite of clopidogrel. (7.3)
- *Cilostazol:* May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction of cilostazol (7.3)
- *Tacrolimus:* Esomeprazole strontium may increase serum levels of tacrolimus (7.5)
- *Methotrexate:* Esomeprazole strontium may increase serum levels of methotrexate (7.7)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Based on animal data, may cause fetal harm (8.1)
- *Nursing Mothers:* Consider discontinuing drug if nursing (8.3)
- *Pediatric Use:* Safety and effectiveness of esomeprazole strontium have not been established in pediatric patients. Not recommended for use in pediatric patients (8.4).
- *Renal Impairment:* Safety of esomeprazole strontium has not been studied in patients with severe renal impairment. Not recommended for use in patients with severe renal impairment (8.6, 12.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Gastroesophageal Reflux Disease (GERD) in Adults

Healing of Erosive Esophagitis

Esomeprazole strontium 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 week course of esomeprazole strontium may be considered.

Maintenance of Healing of Erosive Esophagitis

Esomeprazole strontium is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

Esomeprazole strontium is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults.

1.2 Risk Reduction of NSAID-Associated Gastric Ulcer in Adults

Esomeprazole strontium 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 either due to their age (≥60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

1.3 *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults

Triple Therapy (esomeprazole strontium plus amoxicillin and clarithromycin): esomeprazole strontium, 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 [*see Dosage and Administration (2) and Clinical Studies (14)*].

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 [*see Clinical Pharmacology (12.4) and the prescribing information for clarithromycin*].

1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults

Esomeprazole strontium is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

2 DOSAGE AND ADMINISTRATION

Esomeprazole strontium is supplied as delayed-release capsules for oral administration. The recommended dosages are outlined in Table 1. Esomeprazole strontium 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 Esomeprazole Strontium Delayed-Release Capsules

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD) in Adults		
Healing of Erosive Esophagitis	24.65 mg[a] or 49.3 mg[b]	Once Daily for 4 to 8 Weeks[*]
Maintenance of Healing of Erosive Esophagitis	24.65 mg[a]	Once Daily[**]
Symptomatic Gastroesophageal Reflux Disease	24.65 mg[a]	Once Daily for 4 Weeks[***]
Risk Reduction of NSAID-Associated Gastric Ulcer in Adults	24.65 mg[a] or 49.3 mg[b]	Once Daily for up to 6 months[**]
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults**		
Triple Therapy:		
esomeprazole strontium	49.3 mg[b]	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 in Adults	49.3 mg[†b]	[‡]Twice Daily

[*][*See Clinical Studies (14.1).*] 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.
†The dosage of esomeprazole strontium 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 (7)*].
[a] 24.65 mg of esomeprazole strontium is equivalent to 20 mg of esomeprazole
[b] 49.3 mg of esomeprazole strontium is equivalent to 40 mg of esomeprazole

Refer to amoxicillin and clarithromycin full prescribing information for Contraindications, Warnings, and dosing in elderly and in renally-impaired patients.

Special Populations

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 24.65 mg of esomeprazole strontium (equivalent to 20 mg of esomeprazole) should not be exceeded [*see Clinical Pharmacology (12.3)*].

Administrative Options

Directions for use specific to the route and available methods of administration are presented in Table 2.

Table 2: Administration Options

Administration Options (See text following table for additional instructions.)		
Dosage Form	**Route**	**Options**
Delayed-Release Capsules	Oral	Capsule can be swallowed whole. Do not chew or crush; or Capsule can be opened and granules mixed with applesauce. Do not chew or crush granules.
Delayed-Release Capsules	Nasogastric Tube	Capsule can be opened and the intact granules emptied into a catheter tipped syringe and delivered through the nasogastric tube.

Esomeprazole strontium delayed-release capsules should be swallowed whole. Do not chew or crush capsule.

Alternatively, for patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the esomeprazole strontium 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 strontium 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 strontium 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

Delayed-release capsules: 24.65 mg of esomeprazole strontium (equivalent to 20 mg of esomeprazole) - hard capsules with light pink cap and body containing off white to pale brown granules with HMP 20 printed in black ink.

Delayed-release capsules: 49.3 mg of esomeprazole strontium (equivalent to 40 mg of esomeprazole) - hard capsules with dark pink cap and body containing off white to pale brown granules with HMP 40 printed in black ink.

4 CONTRAINDICATIONS

Esomeprazole strontium is contraindicated in patients with known hypersensitivity to proton pump inhibitors. Hypersensitivity reactions, e.g., angioedema and anaphylactic shock, have been reported with esomeprazole use.

For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with esomeprazole strontium, refer to the CONTRAINDICATIONS section of their package inserts.

5 WARNINGS AND PRECAUTIONS

5.1 Concurrent Gastric Malignancy

Symptomatic response to therapy with esomeprazole strontium does not preclude the presence of gastric malignancy.

5.2 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.

5.3 *Clostridium difficile* Associated Diarrhea

Published observational studies suggest that PPI therapy like esomeprazole strontium 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 [*see Adverse Reactions* (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole strontium, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

5.4 Interaction with Clopidogrel

Avoid concomitant use of esomeprazole strontium with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel 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 inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole strontium, consider alternative anti-platelet therapy [*see Drug Interactions (7.3) and Clinical Pharmacology (12.3)*].

5.5 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)*].

5.6 Hypomagnesemia

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)*].

5.7 Concomitant Use of esomeprazole strontium 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 strontium with St. John's Wort or rifampin.

5.8 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. Providers should temporarily 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.

5.9 Concomitant Use of esomeprazole strontium 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.

The safety of esomeprazole strontium has been established from adequate and well-controlled studies of esomeprazole magnesium *[see Clinical Studies (14)]*. Below is a display of the adverse reactions of esomeprazole magnesium in these adequate and well-controlled studies.

Adults

The safety of esomeprazole magnesium was 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 studies for up to 6–12 months. In general, esomeprazole magnesium was 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 22.3 mg of esomeprazole magnesium (equivalent to 20 mg of esomeprazole), 2,434 patients on 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole), and 3,008 patients on 20 mg of omeprazole 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, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole magnesium or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to esomeprazole magnesium 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 lymphadenopathy, 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 magnesium, 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. There were no differences in types of related adverse reactions 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 were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with esomeprazole magnesium 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 magnesium, 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 magnesium alone.

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions sections.

In clinical trials using combination therapy with esomeprazole magnesium plus amoxicillin and clarithromycin, no additional increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, Adverse Reactions section.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole magnesium. 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;

Hepatobiliary: hepatic failure, hepatitis with or without jaundice;

Immune System: anaphylactic reaction/shock;

Infections and Infestations: GI candidiasis; *Clostridium difficile* associated diarrhea;

Metabolism and nutritional disorders: hypomagnesemia;

Musculoskeletal and Connective Tissue: muscular weakness, myalgia, bone fracture;

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).

7 DRUG INTERACTIONS

7.1 Interference with Antiretroviral Therapy

Concomitant use of atazanavir and nelfinavir with proton pump inhibitors is not recommended. Coadministration 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. Coadministration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.

Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19.

Reduced concentrations of atazanavir and nelfinavir

For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75%, respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended.

Increased concentrations of saquinavir

For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in C_{max} by 75%, and in C_{min} by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily coadministered days 11 to 15. Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

7.2 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. Similar to other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, and erlotinib can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Esomeprazole is an enantiomer of omeprazole. Coadministration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *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, quinidine, clarithromycin, or amoxicillin.

Although drug interaction studies have not shown that esomeprazole has a clinically significant interaction with warfarin, 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 CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

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 esomeprazole strontium with clopidogrel. When using esomeprazole strontium, consider use of alternative anti-platelet therapy [*see Clinical Pharmacology (12.3)*].

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4- 7 times the activity of cilostazol, were increased by 29% and 69% respectively. Coadministration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, 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.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (C_{max} and AUC decreased by 49.6 % and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with esomeprazole strontium.

7.4 Interactions with Investigations of Neuroendocrine Tumors

Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels, which may interfere with investigations for neuroendocrine tumors [*see Warnings and Precautions (5.7) and Clinical Pharmacology (12.2)*].

7.5 Tacrolimus

Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

7.6 Combination Therapy with Clarithromycin

Coadministration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin [*see Clinical Pharmacology (12.4)*].

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due

to drug interactions [*see Warnings and Precautions in prescribing information for clarithromycin*]. Because of these drug interactions, clarithromycin is contraindicated for coadministration with certain drugs [*see Contraindications in prescribing information for clarithromycin*].

7.7 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted [*see Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well controlled studies of esomeprazole strontium delayed-release capsules in pregnant women. Teratogenicity was not observed in an embryofetal developmental study in rats with either esomeprazole strontium or esomeprazole magnesium at equimolar oral doses up to 280 mg esomeprazole/kg/day (about 57 times the daily maximum recommended human dose (MRHD) of 40 mg on a body surface area basis). When administered as either the strontium or magnesium salt, changes in bone morphology and physeal dysplasia were observed in pre- and postnatal developmental toxicity studies in rats at doses equal to or greater than 138 mg esomeprazole/kg/day (approximately 33.6 times the daily MRHD of 40 mg on a body surface area basis). Because of the observed effect at the high doses of esomeprazole strontium on developing bone in rat studies, esomeprazole strontium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

An embryofetal developmental (teratogenicity) study in rats was performed with both esomeprazole strontium and esomeprazole magnesium at equimolar oral doses of 14 to 280 mg esomeprazole/kg/day (about 3.4 to 57 times the daily maximum recommended human dose (MRHD) of 40 mg, on a body surface area basis). At the doses tested, there were no teratogenic or adverse effects on general fetal development or on fetal visceral or skeletal structures. In addition, there was no adverse effect on maternal and fetal bone calcium levels when esomeprazole was administered as either the strontium or magnesium salt. Fetal exposure to strontium and esomeprazole was dose-related.

Pre- and postnatal developmental toxicity studies in rats with additional endpoints to evaluate bone development were performed with both esomeprazole strontium and esomeprazole magnesium at equimolar oral doses of 14 to 280 mg esomeprazole/kg/day (about 3.4 to 57 times the daily MRHD of 40 mg of esomeprazole on a body surface area basis). The rats were fed either a standard diet or a diet with reduced levels of calcium and Vitamin D. When administered as either the strontium or magnesium salt, neonatal/early postnatal (birth to weaning) survival was decreased, body weight and body weight gain were reduced and neurobehavioral or general developmental delays in the immediate post-weaning timeframe were evident at doses equal to or greater than 69 mg esomeprazole/kg/day (about 16.8 times the daily MRHD of 40 mg on a body surface area basis). In addition, when administered as either the strontium or magnesium salt, decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate and minimal to mild bone marrow hypocellularity were noted at doses equal to or greater than 14 mg esomeprazole/kg/day (about 3.4 times the MRHD of 40 mg on a body surface area basis). Physeal dysplasia in the femur was observed in offspring of rats treated with oral doses of esomeprazole (as either the strontium or the magnesium salt) at doses equal to or greater than 138 mg/kg/day (about 33.6 times the daily MRHD of 40 mg on a body surface area basis). No

significant differences were observed between the groups fed nutritionally complete diet and those fed the diet with reduced levels of calcium and Vitamin D.

Adverse effects on maternal bone were observed in pregnant and lactating rats in the pre- and postnatal toxicity studies when esomeprazole strontium or esomeprazole magnesium were administered at equimolar oral doses of 14 to 280 mg esomeprazole/kg/day (about 3.4 to 57 times the daily MRHD of 40 mg on a body surface area basis). When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 138 mg esomeprazole/kg/day (about 33.6 times the daily MRHD of 40 mg on a body surface area basis).

8.3 Nursing Mothers

Limited published data indicate that esomeprazole and strontium are present in human milk. Because of the effect of esomeprazole strontium observed at high doses on developing bone in rat 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 *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of esomeprazole strontium delayed-release capsules have not been established in pediatric patients. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone. Therefore, use in pediatric patients is not recommended because adequate safety studies have not been performed.

In a juvenile rat toxicity study, following administration of either esomeprazole strontium or esomeprazole magnesium at equimolar oral doses of 140 to 280 mg esomeprazole/kg/day (34 to 57 times the daily MRHD of 40 mg on a body surface area basis), increases in deaths were seen at the high dose, along with treatment-related decreases in body weight and body weight gain, decreases in femur weight and femur length and decreases in overall growth *[see Nonclinical Toxicology (13.2)]*.

Symptomatic GERD in infants less than one year of age

A pediatric study of esomeprazole magnesium did not establish efficacy for symptomatic GERD in patients less than 1 year of age. A multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of 98 patients ages 1 to 11 months, inclusive, with symptomatic GERD did not demonstrate a difference between esomeprazole magnesium and placebo.

8.5 Geriatric Use

Of the total number of patients who received esomeprazole magnesium in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥75 years of age.

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.

8.6 Use in Patients with Renal Impairment

No dosage adjustment is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of strontium in patients with severe renal impairment has not been studied and, therefore, use in this patient population is not recommended.

10 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.

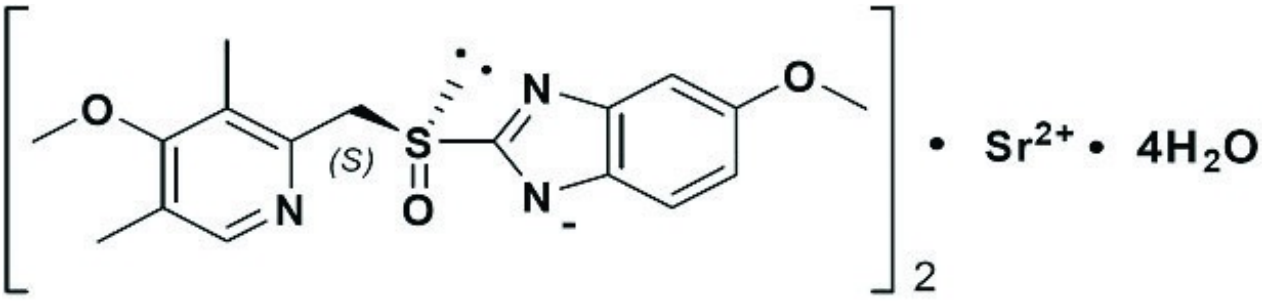
The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 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 (see omeprazole package insert - *Adverse Reactions*). 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.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose contact a Poison Control Center at 1-800-222-1222.

11 DESCRIPTION

The active ingredient in the proton pump inhibitor esomeprazole strontium delayed-release capsules is bis(5 methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) strontium tetrahydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. The molecular formula of esomeprazole strontium is $(C_{17}H_{18}N_3O_3S)_2 \cdot Sr \cdot 4H_2O$ with molecular weight of 848.50. The structural formula is:

Figure 1



The strontium salt is a white or almost white crystalline powder. Each molecule contains 4 moles of water of solvation and is soluble in water.

Esomeprazole strontium is supplied in delayed-release capsules. Each delayed-release capsule contains 24.65 mg esomeprazole strontium equivalent to 20 mg esomeprazole or 49.3 mg esomeprazole strontium equivalent to 40 mg esomeprazole, in the form of enteric-coated granules with the following inactive ingredients: calcium carbonate, hypromellose, methacrylic acid copolymer dispersion, mono- and diglycerides, polysorbate 80, sugar spheres, talc, triethyl citrate. The 24.65 mg capsule shells have the following inactive ingredients: gelatin, titanium dioxide, synthetic iron oxide. The 49.3 mg capsule shells have the following inactive ingredients: gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6.

Each 24.65 mg capsule contains 2.6 mg of strontium. Each 49.3 mg capsule contains 5.1 mg of strontium.

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 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.

12.2 Pharmacodynamics

Antisecretory Activity

The effect of esomeprazole magnesium on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole) and 22.3 mg of esomeprazole magnesium (equivalent to 20 mg of esomeprazole) were administered over 5 days. The results are shown in Table 3:

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

Parameter	esomeprazole magnesium 44.6 mg	esomeprazole magnesium 22.3 mg
% Time Gastric pH >4[†] (Hours)	70%[*] (16.8 h)	53% (12.7 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 44.6 mg vs. esomeprazole magnesium 22.3 mg

In a second study, the effect on intragastric pH of esomeprazole magnesium 44.6 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 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.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid 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 H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients treated with omeprazole 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 (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 had no effect on thyroid function when given in oral doses of 22.3 mg or 44.6 mg for 4 weeks. Other effects of esomeprazole on the endocrine system were assessed using omeprazole studies. Omeprazole 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, cholecystokinin, or secretin.

12.3 Pharmacokinetics

Absorption

Following single oral administration of esomeprazole strontium delayed-release capsules 49.3 mg (equivalent to 40 mg of esomeprazole) in 36 healthy adults under fasting conditions, the peak plasma concentrations (Cmax) of esomeprazole occurred at approximately 1.7 hours post-dose. Mean esomeprazole Cmax and area under the plasma concentration–time curve (AUC) were comparable to those for esomeprazole magnesium delayed-release capsules 44.6 mg (equivalent to 40 mg of esomeprazole). In a study using esomeprazole magnesium delayed-release capsules, esomeprazole Cmax increased proportionally when the dose was increased, and there was a three-fold increase in esomeprazole AUC when the dose was increased from 22.3 mg (equivalent to 20 mg of esomeprazole) to 44.6 mg. Systemic bioavailability will increase following multiple dosing and esomeprazole AUC is expected to increase to approximately 2.6-fold after once daily dosing of esomeprazole strontium delayed-release capsules 49.3 mg for 5 days.

In one single dose study in 39 healthy adult subjects under fasting conditions, the capsule contents of esomeprazole strontium delayed-release capsules 49.3 mg were sprinkled onto one tablespoon of applesauce, mean esomeprazole Cmax and AUC were comparable to those for esomeprazole magnesium delayed-release capsules 44.6 mg administered under the same conditions. In a food-effect study, the AUC after administration of a single 49.3 mg dose of esomeprazole strontium delayed-release capsules decreased by 52% after a high fat meal compared to fasting conditions. Esomeprazole strontium delayed-release capsules should be taken at least one hour before meals.

Table 4: Pharmacokinetic Parameters of Esomeprazole Following Single Oral Administration in Healthy Adult Volunteers under Fasting Conditions

Parameters	**Esomeprazole strontium delayed-release capsules 49.3 mg**		**Esomeprazole strontium delayed-release capsules 49.3 mg (with one tablespoon of apple sauce[a])**	
	Mean[b]	**SD**	**Mean[b]**	**SD**
C_{max} (ng/mL)	1105.6	464.8	1155.6	429.8
T_{max} (h)	1.7		2.3	
$AUC_{0\text{-}tlast}$ (ng*h/Ml)	2283.9	1400.4	2389.1	1071.4
$AUC_{0\text{-}\infty}$ (ng*h/mL)	2310.9	1428.3	2417.8	1081.8

[a]Capsule contents were administered with one tablespoon of applesauce under otherwise fasting conditions.
[b]Values represent the arithmetic mean, except T_{max}, which is the median.

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, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 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.

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.

Combination Therapy with Antimicrobials

Esomeprazole magnesium 44.6 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady-state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively, during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during coadministration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

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 magnesium 44.6 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. Pharmacodynamic 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.

Special Populations

Geriatric

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

Gender

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

Hepatic Insufficiency

The steady state pharmacokinetics of esomeprazole obtained after administration of esomeprazole magnesium 44.6 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 esomeprazole 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) esomeprazole strontium dose of 24.65 mg once daily should not be exceeded [*see Dosage and Administration (2)*].

Renal Insufficiency

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. In a study with a different strontium product and dose in patients with mild to moderate renal impairment, strontium clearance was reduced with the decrease in creatinine clearance. The pharmacokinetics of strontium in patients with severe renal impairment has not been characterized [*see Use in Specific Populations (8.6)*].

Other pharmacokinetic observations

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Studies evaluating concomitant administration of esomeprazole magnesium 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.

12.4 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 [*see Indications and Usage (1) and Clinical Studies (14)*].

Helicobacter pylori: Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Pretreatment Resistance: Clarithromycin pretreatment resistance rate (MIC ≥1 mcg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of >99% (394/395) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤0.25 mcg/mL) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolate with an amoxicillin MIC = 0.5 mcg/mL.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in Table 5:

Table 5: Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a] for Triple Therapy - (esomeprazole magnesium 44.6 mg[#] once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days)

Clarithromycin Pretreatment Results	***H. pylori* negative (Eradicated)**	***H. pylori* positive (Not Eradicated) Post-treatment susceptibility results**			
		S[b]	**I[b]**	**R[b]**	**No MIC**
Susceptible[b] 182	162	4	0	2	14
Intermediate[b] 1	1	0	0	0	0
Resistant[b] 29	13	1	0	13	2

[a]Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results
[b]Susceptible (S) MIC ≤0.25 mcg/mL, Intermediate (I) MIC = 0.5 mcg/mL, Resistant (R) MIC ≥1.0 mcg/mL
[#] 44.6 mg of esomeprazole magnesium is equivalent to 40 mg of esomeprazole

Patients not eradicated of *H. pylori* following esomeprazole magnesium/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes:

In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤0.25 mcg/mL) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of *H. pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

Susceptibility Test for Helicobacter pylori: For susceptibility testing information about *Helicobacter pylori*, see Microbiology section in prescribing information for clarithromycin and amoxicillin.

Effects on Gastrointestinal Microbial Ecology: Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using studies of omeprazole, of which esomeprazole is an enantiomer. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44, and 141 mg/kg/day (about 0.7 to 57 times the human dose of 20 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 omeprazole. 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 omeprazole/kg/day (about 5.6 times the human dose 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 difference between treated and control rats was much 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 omeprazole did not show increased tumor occurrence, but the study was not conclusive.

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

The potential effects of esomeprazole strontium on fertility and reproductive performance were not directly studied. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 33.6 times the daily MRHD of 40 mg 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

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole strontium or esomeprazole magnesium at equimolar oral doses of 70 to 280 mg esomeprazole/kg/day (about 17 to 57 times the daily MRHD of 40 mg on a body surface area basis). When administered as either the strontium or magnesium salt from postnatal day 7 through postnatal day 35, the dose of 280 mg esomeprazole/kg/day produced an increase in the number of deaths. In addition, when administered as either the strontium or magnesium salt, doses equal to or greater than 140 mg esomeprazole/kg/day (about 34 times the daily MRHD 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.

14 CLINICAL STUDIES

The safety and efficacy of esomeprazole strontium has been established based on adequate and well-controlled adult studies of esomeprazole magnesium in the healing and maintenance of erosive esophagitis, symptomatic GERD, risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Below is a display of the results of the adequate and well-controlled studies of esomeprazole magnesium in these conditions.

14.1 Healing of Erosive Esophagitis

The healing rates of 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole), 22.3 mg of esomeprazole magnesium (equivalent to 20 mg of esomeprazole), and 20 mg of omeprazole (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 Table 6:

Table 6: Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level*
1	588	Esomeprazole magnesium 22.3 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	Esomeprazole magnesium 44.6 mg	75.9%	94.1%	$p < 0.001$
	656	Esomeprazole magnesium 22.3 mg	70.5%	89.9%	$p < 0.05$
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	Esomeprazole magnesium 44.6 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	Esomeprazole magnesium 44.6 mg	81.7%	93.7%	$p < 0.001$
	1209	Omeprazole 20 mg	68.7%	84.2%	

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

In these same studies of patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in Table 7:

Table 7: Sustained Resolution‡ of Heartburn (Erosive Esophagitis Patients)

			Cumulative Percent# with Sustained Resolution		
Study	No. of Patients	Treatment Groups	Day 14	Day 28	Significance Level*
1	573	Esomeprazole magnesium 22.3 mg	64.3%	72.7%	N.S.

1	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	Esomeprazole magnesium 44.6 mg	64.8%	74.2%	p <0.001
	620	Esomeprazole magnesium 22.3 mg	62.9%	70.1%	N.S.
	626	Omeprazole 20 mg	56.5%	66.6%	
3	568	Esomeprazole magnesium 44.6 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	Esomeprazole magnesium 44.6 mg	67.6%	75.1%	p <0.001
	1188	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 start 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 5 days for esomeprazole magnesium 44.6 mg, 7 to 8 days for esomeprazole magnesium 22.3 mg and 7 to 9 days for omeprazole 20 mg.

There are no comparisons of 44.6 mg of esomeprazole magnesium with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

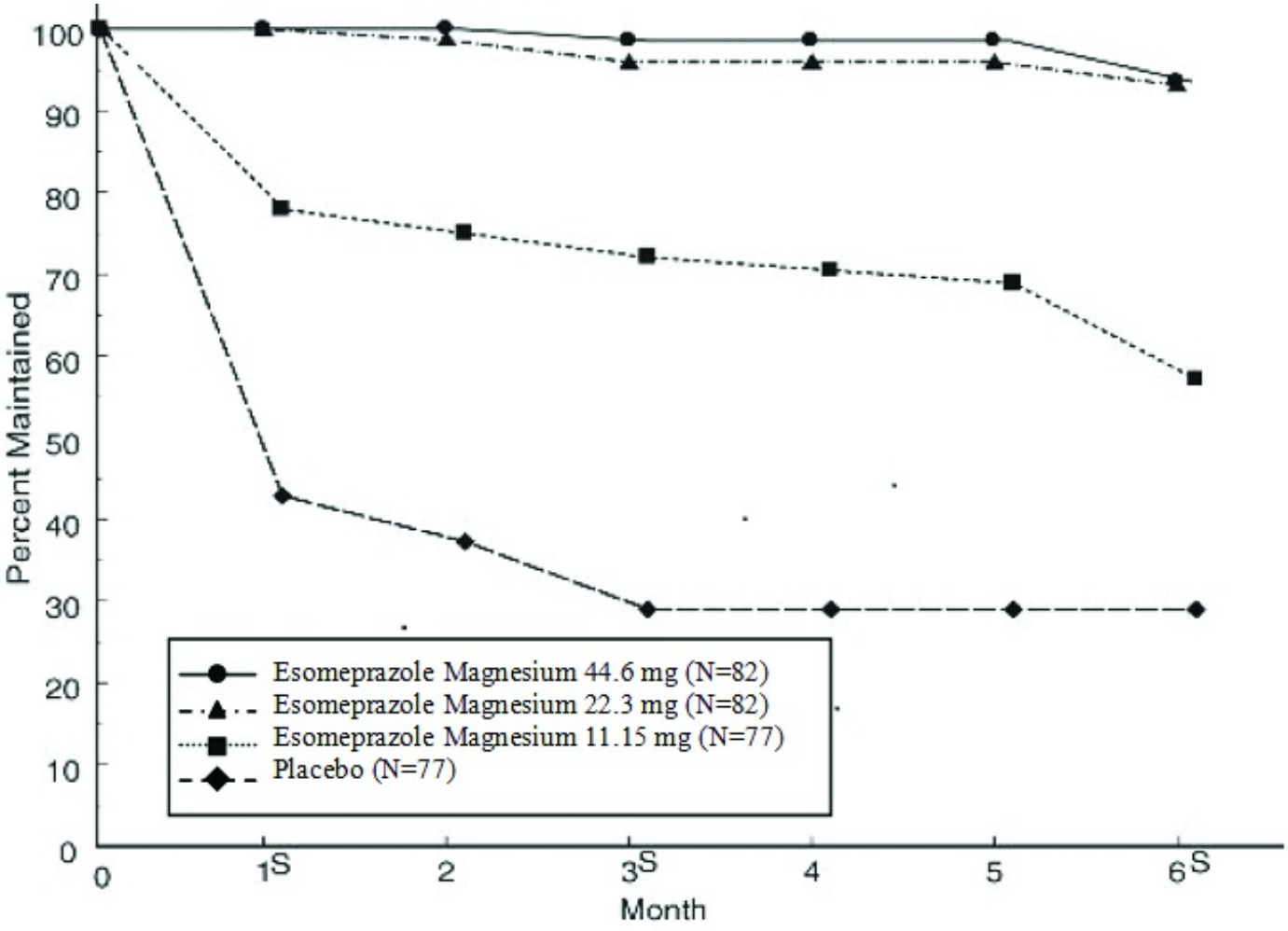
Long-Term Maintenance of Healing of Erosive Esophagitis

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate esomeprazole magnesium 44.6 mg (n=174), 22.3 mg (n=180), 11.15 mg (n=168) or placebo (n=171) once daily over six months of treatment.

No additional clinical benefit was seen with esomeprazole magnesium 44.6 mg over esomeprazole magnesium 22.3 mg.

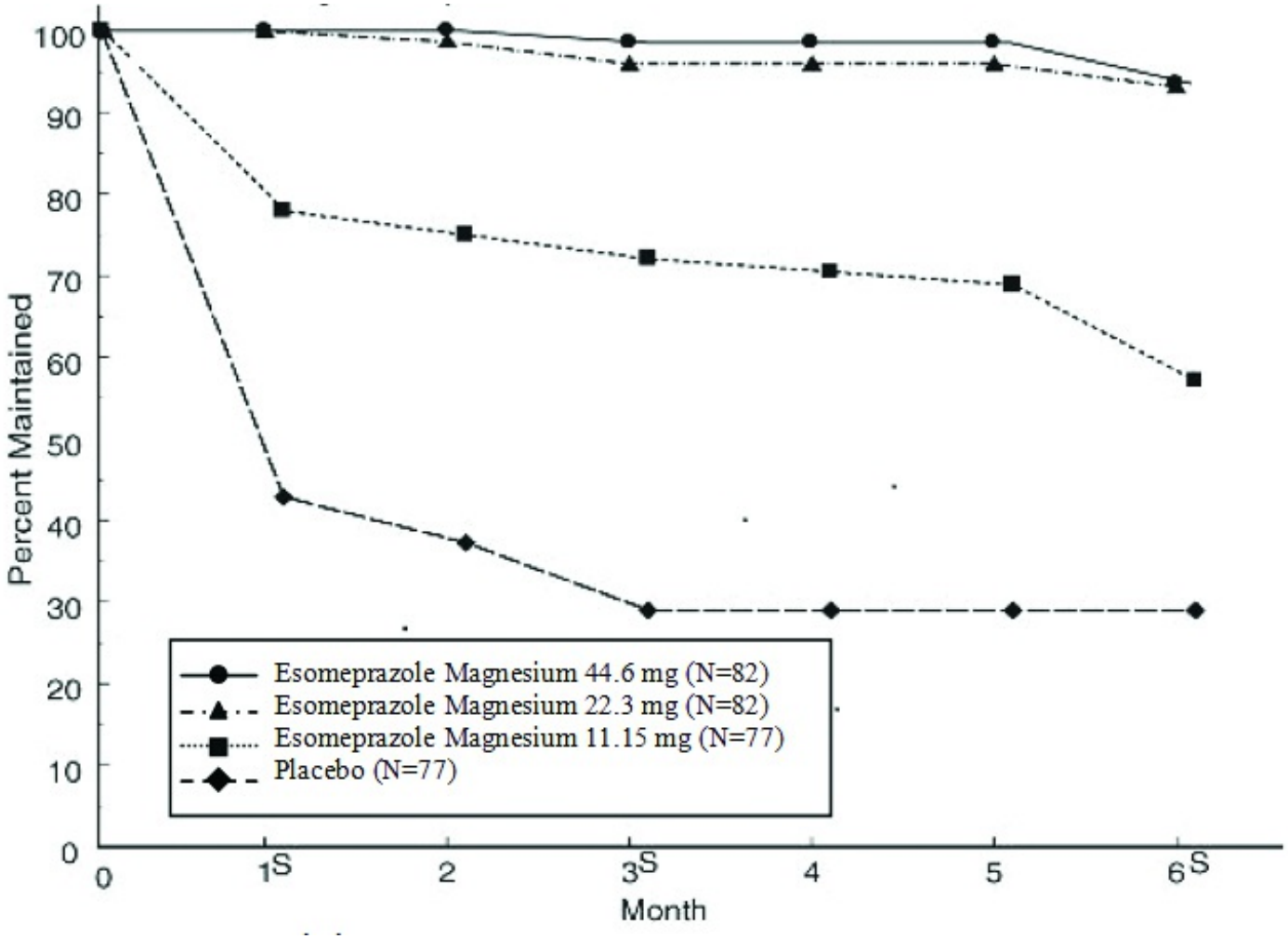
The percentages of patients that maintained healing of erosive esophagitis at the various time points are shown in the Figures 2 and 3:

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



s = scheduled visit

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



s= 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 compared to placebo.

In both studies, the proportion of patients on esomeprazole magnesium 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 44.6 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 22.3 mg or 44.6 mg of esomeprazole magnesium (equivalent to 20 mg or 40 mg of esomeprazole, respectively) once daily versus placebo for resolution of GERD symptoms. Patients had ≥ 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 groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

No additional clinical benefit was seen with esomeprazole magnesium 44.6 mg over esomeprazole magnesium 22.3 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) - Esomeprazole Magnesium

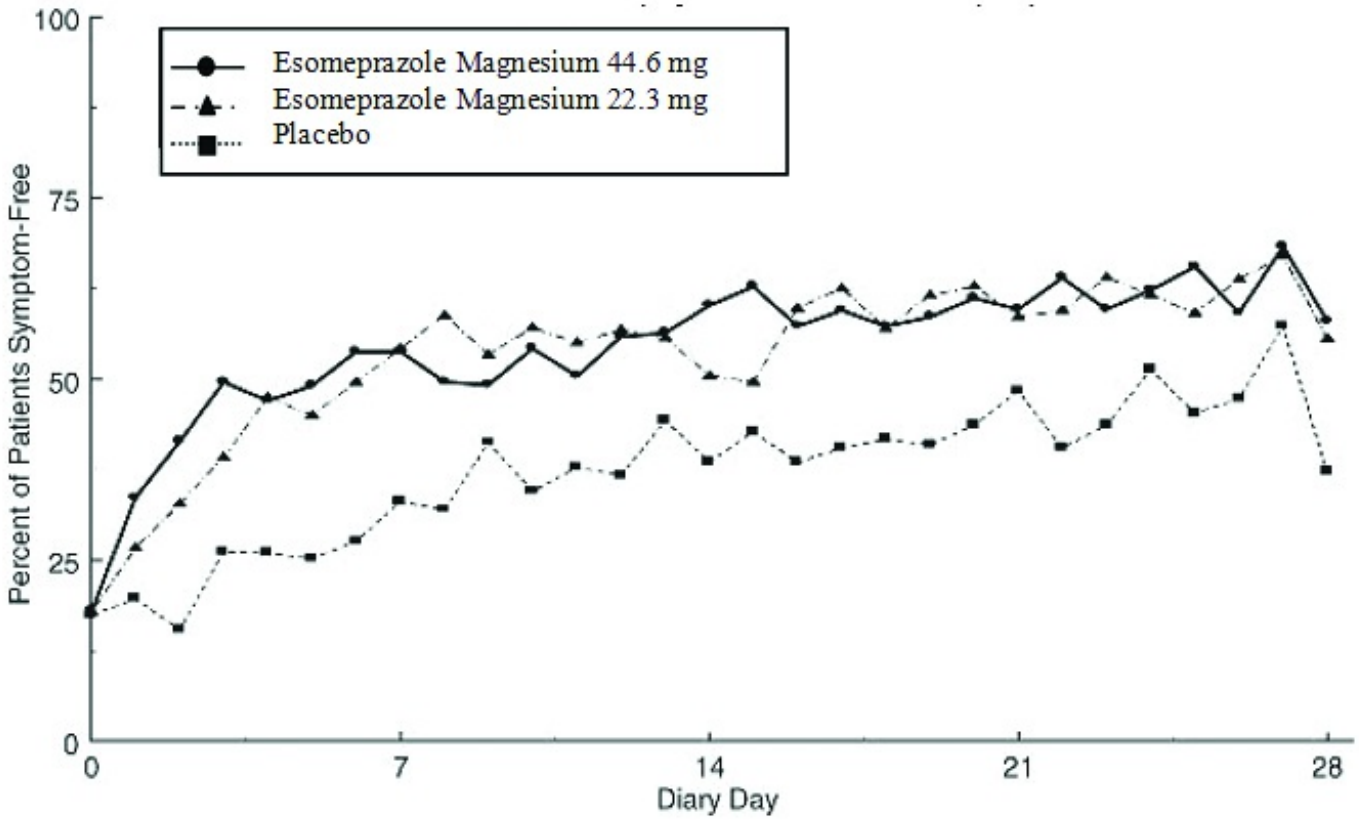
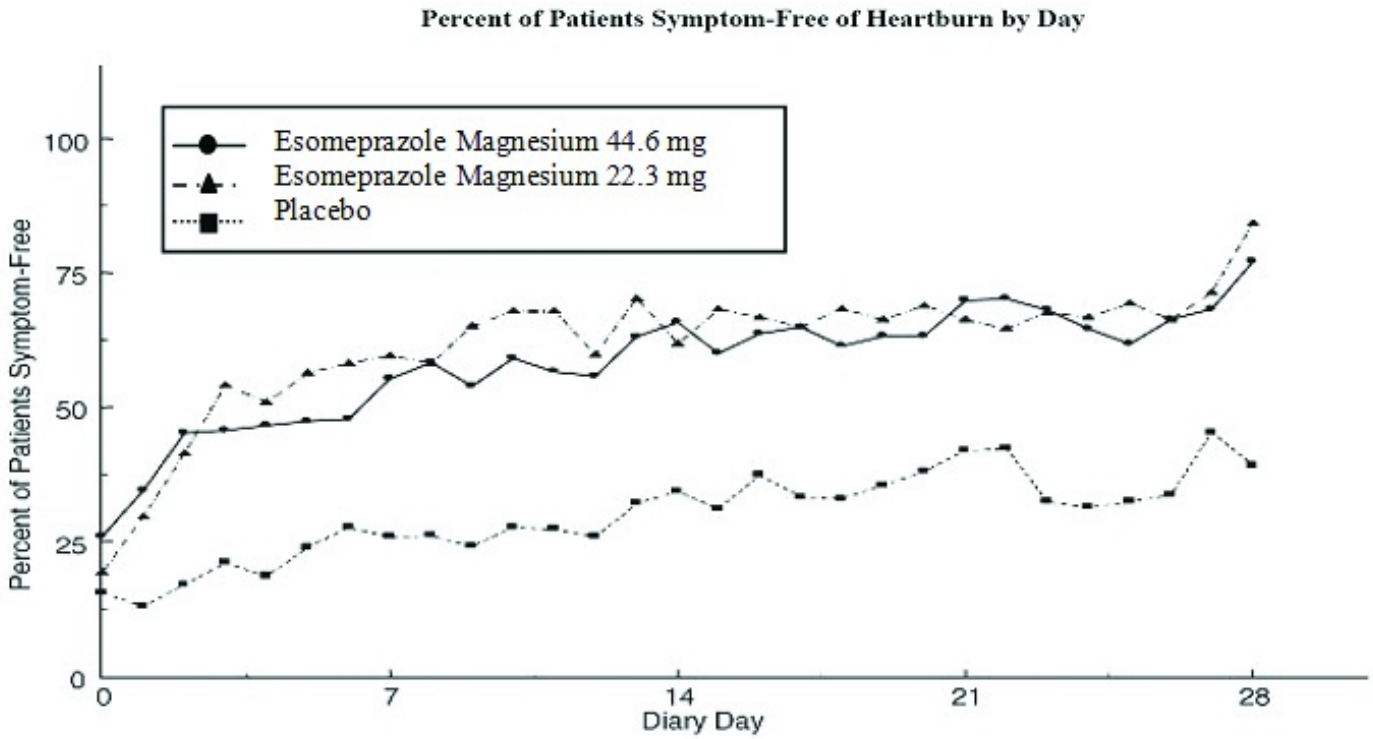


Figure 5: Percent of Patients Symptom-Free of Heartburn by Day (Study 226) - Esomeprazole Magnesium



In three European symptomatic GERD trials, esomeprazole magnesium 22.3 mg and 44.6 mg and omeprazole 20 mg were evaluated. No significant treatment related differences were seen.

14.3 Risk Reduction of NSAID-Associated Gastric Ulcer

Two multicenter, double-blind, placebo-controlled studies were conducted in patients at risk of developing gastric and/or duodenal ulcers associated with continuous use of non-selective and COX-2 selective NSAIDs. A total of 1429 patients were randomized across the 2 studies. Patients ranged in age from 19 to 89 (median age 66.0 years) with 70.7% female, 29.3% male, 82.9% Caucasian, 5.5% Black, 3.7% Asian, and 8% Others. At baseline, the patients in these studies were endoscopically confirmed not to have ulcers but were determined to be at risk for ulcer occurrence due to their age (≥60 years) and/or history of a documented gastric or duodenal ulcer within the past 5 years. Patients receiving NSAIDs and treated with 22.3 mg or 44.6 mg of esomeprazole magnesium (equivalent to 20 mg or 40 mg of esomeprazole, respectively) once a day experienced significant reduction in gastric ulcer occurrences relative to placebo treatment at 26 weeks. See Table 8. No additional benefit was seen with esomeprazole magnesium 44.6 mg over esomeprazole magnesium 22.3 mg. These studies did not demonstrate significant reduction in the development of NSAID-associated duodenal ulcer. The incidence of duodenal ulcers in these trials was low.

Table 8: Cumulative Percentage of Patients without Gastric Ulcers at 26 Weeks

Study	No. of Patients	Treatment Group	% of Patients Remaining Gastric Ulcer Free*
1	191	esomeprazole magnesium 22.3 mg	95.4
	194	esomeprazole magnesium 44.6 mg	96.7
	184	Placebo	88.2
2	267	esomeprazole magnesium 22.3 mg	94.7
	271	esomeprazole magnesium 44.6 mg	95.3
	257	Placebo	83.3

* %=Life Table Estimate. Significant difference from placebo ($p<0.01$).

14.4 *Helicobacter pylori* (*H. pylori*) Eradication in Patients with Duodenal Ulcer Disease

Triple Therapy (esomeprazole magnesium/amoxicillin/clarithromycin): Two multicenter, randomized, double-blind studies were conducted using a 10 day treatment regimen. The first study (191) compared 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole) once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to 44.6 mg of esomeprazole magnesium once daily plus clarithromycin 500 mg twice daily. The second study (193) compared 44.6 mg of esomeprazole magnesium once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to 44.6 mg of esomeprazole magnesium once daily. *H. pylori* eradication rates, defined as at least two negative tests and no positive tests from CLOtest®, histology and/or culture at 4 weeks post-therapy, were significantly higher in the esomeprazole magnesium plus amoxicillin and clarithromycin group than in the esomeprazole magnesium plus clarithromycin or esomeprazole magnesium alone group. The results are shown in Table 9:

Table 9: *H. pylori* Eradication Rates at 4 Weeks after 10 Day Treatment Regimen

% of Patients Cured [95% Confidence Interval] (Number of Patients)			
Study	**Treatment Group**	**Per-Protocol†**	**Intent-to-Treat‡**
191	esomeprazole magnesium plus amoxicillin and clarithromycin	84%* [78, 89] (n=196)	77%* [71, 82] (n=233)
	esomeprazole magnesium plus	55%	52%

	clarithromycin	[48, 62] (n=187)	[45, 59] (n=215)
193	esomeprazole magnesium plus amoxicillin and clarithromycin	85%** [74, 93] (n=67)	78%** [67, 87] (n=74)
	esomeprazole magnesium	5% [0, 23] (n=22)	4% [0, 21] (n=24)

†Patients were included in the analysis if they had *H. pylori* infection documented at baseline, had at least one endoscopically verified duodenal ulcer ≥0.5 cm in diameter at baseline or had a documented history of duodenal ulcer disease within the past 5 years, and were not protocol violators. Patients who dropped out of the study due to an adverse reaction related to the study drug were included in the analysis as not *H. pylori* eradicated.

‡Patients were included in the analysis if they had documented *H. pylori* infection at baseline, had at least one documented duodenal ulcer at baseline, or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as not *H. pylori* eradicated.

*$p < 0.05$ compared to esomeprazole magnesium plus clarithromycin

**$p < 0.05$ compared to esomeprazole magnesium alone

The percentage of patients with a healed baseline duodenal ulcer by 4 weeks after the 10 day treatment regimen in the esomeprazole magnesium plus amoxicillin and clarithromycin group was 75% (n=156) and 57% (n=60) respectively, in the studies 191 and 193 (per-protocol analysis).

14.5 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In a multicenter, open-label dose-escalation study of 21 patients (15 males and 6 females, 18 Caucasian and Black, mean age of 55.5 years) with pathological hypersecretory conditions, such as Zollinger-Ellison Syndrome, esomeprazole magnesium significantly inhibited gastric acid secretion. Initial dose was 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole) twice daily in 19/21 patients and 89.2 mg of esomeprazole magnesium (equivalent to 80 mg of esomeprazole) twice daily in 2/21 patients. Total daily esomeprazole magnesium doses ranging from 89.2 mg to 267.6 mg (equivalent to 240 mg of esomeprazole) for 12 months maintained gastric acid output below the target levels of 10 mEq/h in patients without prior gastric acid-reducing surgery and below 5 mEq/hr in patients with prior gastric acid-reducing surgery. At the Month 12 final visit, 18/20 (90%) patients had Basal Acid Output (BAO) under satisfactory control (median BAO = 0.17 mmol/hr). Of the 18 patients evaluated with a starting dose of 40 mg twice daily, 13 (72%) had their BAO controlled with the original dosing regimen at the final visit. See Table 10.

Table 10: Adequate Acid Suppression at Final Visit by Dose Regimen

Esomeprazole magnesium dose at the Month 12 visit	BAO under adequate control at the Month 12 visit (N=20)*
44.6 mg twice daily	13/15
89.2 mg twice daily	4/4
89.2 mg three times daily	1/1

*One patient was not evaluated.

16 HOW SUPPLIED/STORAGE AND HANDLING

Esomeprazole strontium delayed-release capsules, 24.65 mg (equivalent to 20 mg of esomeprazole), are hard capsules with light pink cap and body containing off-white to pale brown granules with HMP 20 printed in black ink.

They are available as follows:

Unit of use bottles of 30 NDC 65162-955-03

Esomeprazole strontium delayed-release capsules, 49.3 mg (equivalent to 40 mg of esomeprazole), are hard capsules with dark pink cap and body containing off-white to pale brown granules with HMP 40 printed in black ink.

They are available as follows:
Unit of use bottles of 30 NDC 65162-957-03

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep esomeprazole strontium delayed-release capsules container tightly closed. Dispense in a tight container if the esomeprazole strontium delayed-release capsules product package is subdivided.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

- Advise patients to let you know if they are taking, or begin taking, other medications, because esomeprazole strontium delayed-release capsules can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [*see Drug Interactions (7.1)*].
- Advise patients to let you know if they have kidney or liver disease [*see Use in Specific Populations (8.6),see Clinical Pharmacology (12.3)*].
- Let patients know that antacids may be used while taking esomeprazole strontium delayed-release capsules.
- Advise patients to take esomeprazole strontium delayed-release capsules at least one hour before a meal.
- For patients who are prescribed esomeprazole strontium delayed-release capsules, advise them not to chew or crush the capsules.
- Advise patients that, if they open esomeprazole strontium delayed-release capsules to mix the granules with food, the granules should only be mixed with applesauce. Use with other foods has not been evaluated and is not recommended.
- For patients who are advised to open the esomeprazole strontium delayed-release capsules before taking them, instruct them in the proper technique for administration [*see Dosage and Administration (2)*] and tell them to follow the dosing instructions in the PATIENT INFORMATION insert included in the package.
- Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [*see Warnings and Precautions (5.3)*].
- Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [*see Warnings and Precautions (5.6)*].

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MEDICATION GUIDE

ESOMEPRAZOLE STRONTIUM (es-o-mep-ra-zol stron-tee-um)

delayed-release capsules

Read the Medication Guide that comes with esomeprazole strontium before you start taking esomeprazole strontium and each time you get a refill. There may be new information. This information

does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about esomeprazole strontium?

Esomeprazole strontium may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.

Esomeprazole strontium can cause serious side effects, including:

- **Diarrhea**. Esomeprazole strontium may increase your risk of getting severe diarrhea. This diarrhea may be caused by an infection *(Clostridium difficile)* in your intestines.

Call your doctor right away if you have watery stool, stomach pain, and fever that does not go away.

- **Bone fractures**. People who take multiple daily doses of Proton Pump Inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist, or spine. You should take esomeprazole strontium exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take esomeprazole strontium.

Esomeprazole strontium can have other serious side effects. See **"What are the possible side effects of esomeprazole strontium?"**

What is esomeprazole strontium?

Esomeprazole strontium is a prescription medicine called a proton pump inhibitor (PPI). Esomeprazole strontium reduces the amount of acid in your stomach.

Esomeprazole strontium is used in adults:

- for 4 to 8 weeks to treat the symptoms of gastroesophageal reflux disease (GERD). Esomeprazole strontium may also be prescribed to heal acid-related damage to the lining of the esophagus (erosive esophagitis), and to help continue this healing.
  GERD happens when acid in your stomach backs up into the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste, or burping.
- for up to 6 months to reduce the risk of stomach ulcers in some people taking pain medicines called non-steroidal anti-inflammatory drugs (NSAIDs)
- to treat patients with a stomach infection (Helicobacter pylori), along with the antibiotics amoxicillin and clarithromycin
- for the long-term treatment of conditions where your stomach makes too much acid, including Zollinger-Ellison Syndrome. Zollinger-Ellison Syndrome is a rare condition in which the stomach produces a more than normal amount of acid.

It is not known if esomeprazole strontium is safe and effective in children. Esomeprazole strontium should not be used in children.

Who should not take esomeprazole strontium?

Do not take esomeprazole strontium if you:

- are allergic to esomeprazole strontium or any of the ingredients in esomeprazole strontium. See the end of this Medication Guide for a complete list of ingredients in esomeprazole strontium.
- are allergic to any other Proton Pump Inhibitor (PPI) medicine

What should I tell my doctor before taking esomeprazole strontium?

Before you take esomeprazole strontium, tell your doctor if you:

- have been told that you have low magnesium levels in your blood
- have liver problems
- have kidney problems. You should not take esomeprazole strontium if you have severe kidney problems.

- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if esomeprazole strontium can harm your unborn baby.
- are breastfeeding or planning to breastfeed. Esomeprazole strontium passes into your breast milk. You and your doctor should decide if you will take esomeprazole strontium or breastfeed. You should not do both. Talk to your doctor about the best way to feed your baby if you take esomeprazole strontium.

Tell your doctor about all of the medicines you take, including prescription and non-prescription drugs, vitamins and herbal supplements. Esomeprazole strontium may affect how other medicines work, and other medicines may affect how esomeprazole strontium works.

Especially tell your doctor if you take:
- warfarin (Coumadin, Jantoven)
- ketoconazole (Nizoral)
- voriconazole (Vfend)
- atazanavir (Reyataz)
- nelfinavir (Viracept)
- saquinavir (Fortovase)
- products that contain iron
- digoxin (Lanoxin)
- St.John's Wort (*Hypericum perforatum*)
- rifampin (Rimactane, Rifater, Rifamate)
- cilostazol (Pletal)
- diazepam (Valium)
- tacrolimus (Prograf)
- erlotinib (Tarceva)
- methotrexate
- clopidogrel (Plavix)

How should I take esomeprazole strontium?
- Take esomeprazole strontium exactly as prescribed by your doctor.
- Do not change your dose or stop esomeprazole strontium without talking to your doctor.
- Take esomeprazole strontium at least 1 hour before a meal.
- Swallow esomeprazole strontium delayed-release capsules whole. **Never chew or crush esomeprazole strontium delayed-release capsules.**
- If you have difficulty swallowing esomeprazole strontium, you may open the capsule and empty the contents into a tablespoon of applesauce. Esomeprazole strontium should only be mixed with applesauce. The applesauce should not be hot, and it should be soft enough so that you can swallow it without chewing. Mix the contents with the applesauce. Do not crush or chew the granules. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you take too much esomeprazole strontium, call your doctor or local poison control center right away, or go to the nearest hospital emergency room.
- See the "Instructions for Use" at the end of this Medication Guide for instructions about how to mix and give esomeprazole strontium through a nasogastric tube.

What are the possible side effects of esomeprazole strontium?

Esomeprazole strontium can cause serious side effects, including:
- **See "What is the most important information I should know about esomeprazole strontium?"**
- **Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis).** Using esomeprazole strontium for a long period of time may increase the risk of inflammation to your stomach lining. You may or may not have symptoms. Tell your doctor if you have stomach pain,

nausea, vomiting, or weight loss.
- **Low magnesium levels in your body**. This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.

Tell your doctor right away if you have any of these symptoms:
- seizures
- dizziness
- abnormal or fast heart beat
- jitteriness
- jerking movements or shaking (tremors)
- muscle weakness
- spasms of the hands and feet
- cramps or muscle aches
- spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking esomeprazole strontium or during treatment if you will be taking esomeprazole strontium for a long period of time.

The most common side effects with esomeprazole strontium may include:
- headache
- diarrhea
- nausea
- gas
- abdominal pain
- constipation
- dry mouth

Other side effects:

Serious allergic reactions. Tell your doctor if you get any of the following symptoms with esomeprazole strontium:
- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop esomeprazole strontium if these symptoms happen.

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the possible side effects with esomeprazole strontium.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store esomeprazole strontium?
- Store esomeprazole strontium at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the container of esomeprazole strontium closed tightly.

Keep esomeprazole strontiumand all medicines out of the reach of children.

General information about esomeprazole strontium

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use esomeprazole strontium for a condition for which it was not prescribed. Do not give esomeprazole

strontium to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about esomeprazole strontium. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about esomeprazole strontium that is written for health professionals.

For more information, go to www.amneal.com or call 1-877-835-5472.

What are the ingredients in esomeprazole strontium?

Active ingredient: esomeprazole strontium tetrahydrate

Inactive ingredients:calcium carbonate, hypromellose, methacrylic acid copolymer dispersion, mono- and diglycerides, polysorbate 80, sugar spheres, talc, triethyl citrate.

The 24.65 mg capsule shells contain: gelatin, titanium dioxide, synthetic iron oxide.

The 49.3 mg capsule shells contain: gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #40, FD&C Yellow #6.

Instructions for Use

For instructions on taking esomeprazole strontium delayed-release capsules, see the section of this Medication Guide called "**How should I take esomeprazole strontium?**"

Esomeprazole strontium delayed-release capsules may be given through a nasogastric tube (NG tube) as prescribed by your doctor. Follow the instructions below:

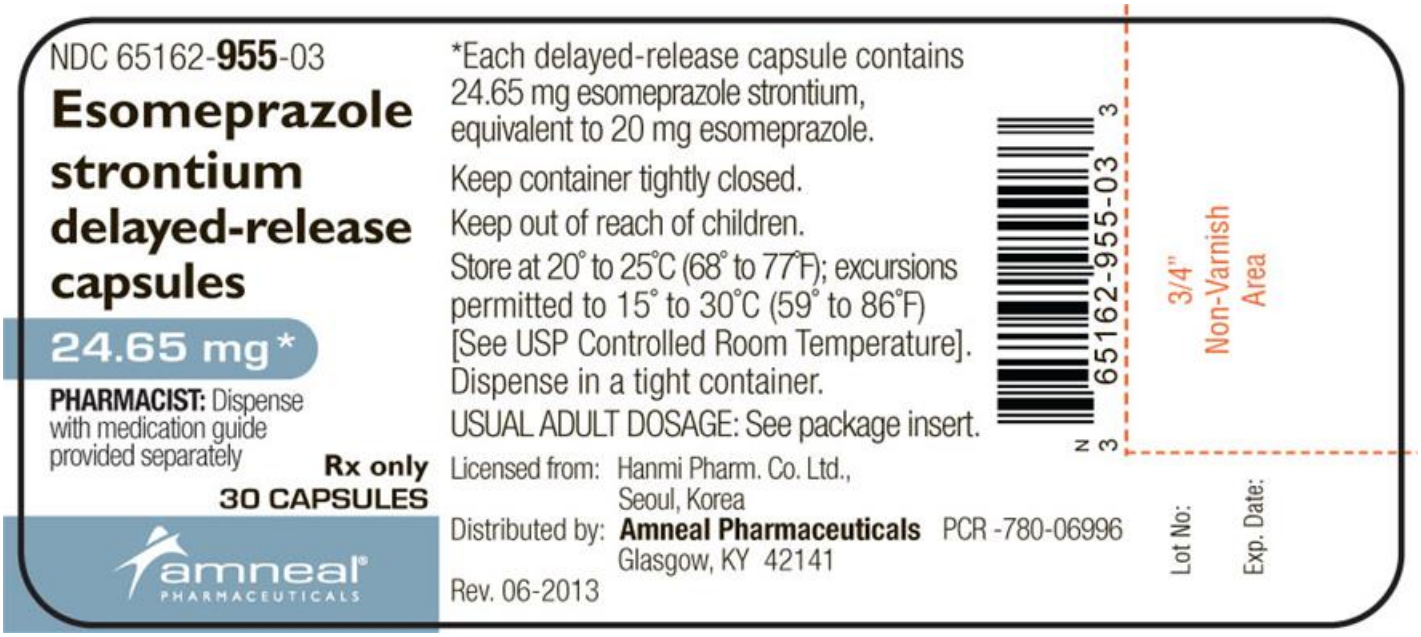
- Open the capsule and empty the granules into a 60 mL catheter tipped syringe. Mix with 50 mL of water. Use only a catheter tipped syringe to give esomeprazole strontium through a NG tube.
- Replace the plunger and shake the syringe well for 15 seconds. Hold the syringe with the tip up and check for granules in the tip.
- Give the medicine right away.
- Do not give the granules if they have dissolved or have broken into pieces.
- Attach the syringe to the NG tube. Give the medicine in the syringe through the NG tube into the stomach.
- After giving the granules, flush the NG tube with more water.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Amneal Pharmaceuticals, Glasgow, KY 42141

Issued: August 2013

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



ESOMEPRAZOLE STRONTIUM

esomeprazole strontium capsule, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65162-955
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESOMEPRAZOLE STRONTIUM (UNII: C5N25H3803) (ESOMEPRAZOLE - UNII:N3PA6559FT)	ESOMEPRAZOLE	20 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM CARBONATE (UNII: H0G9379FGK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
METHACRYLIC ACID (UNII: 1CS02G8656)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	PINK (light pink)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	HMP20
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65162-955-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	08/12/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA202342	08/12/2013	

ESOMEPRAZOLE STRONTIUM

esomeprazole strontium capsule, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65162-957
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESOMEPRAZOLE STRONTIUM (UNII: C5N25H3803) (ESOMEPRAZOLE - UNII:N3PA6559FT)	ESOMEPRAZOLE	40 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM CARBONATE (UNII: H0G9379FGK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
METHACRYLIC ACID (UNII: 1CS02G8656)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	PINK (dark pink)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	HMP40
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65162-957-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	08/12/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA202342	08/12/2013	

Labeler - Amneal Pharmaceuticals LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions, LLC		829672745	ANALYSIS(65162-955, 65162-957) , MANUFACTURE(65162-955, 65162-957)

Revised: 12/2019 Amneal Pharmaceuticals LLC