

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugs>

*Each delayed-release capsule contains 22.25 mg of esomeprazole magnesium, USP equivalent to 20 mg of esomeprazole.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured for:

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

Made in India

 **Mylan®**

Mylan.com

RMX23510H

NDC 0378-2350-93

**Esomeprazole
Magnesium
Delayed-release
Capsules, USP**

20 mg*



PHARMACIST: Dispense the accompanying Medication Guide to each patient.

 **Mylan®**

Rx only

30 Capsules



Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

**NO VARNISH
ZONE**



This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

*Each delayed-release capsule contains 22.25 mg of esomeprazole magnesium, USP equivalent to 20 mg of esomeprazole.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

This container is not intended for dispensing for household use.

Manufactured for:
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 **Mylan**[®] | Mylan.com

NDC 0378-2350-10

**Esomeprazole
Magnesium
Delayed-release
Capsules, USP**

20 mg*

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

 **Mylan**[®]

Rx only

1000 Capsules



Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

**NO VARNISH
ZONE**



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*Each delayed-release capsule contains 44.50 mg of esomeprazole magnesium, USP equivalent to 40 mg of esomeprazole.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

 **Mylan**[®]
Mylan.com

RMX2351H

NDC 0378-2351-93

**Esomeprazole
Magnesium
Delayed-release
Capsules, USP**

40 mg*



PHARMACIST: Dispense the accompanying Medication Guide to each patient.

 **Mylan**[®]

Rx only

30 Capsules



Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

**NO VARNISH
ZONE**



This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

*Each delayed-release capsule contains 44.50 mg of esomeprazole magnesium, USP equivalent to 40 mg of esomeprazole.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

This container is not intended for dispensing for household use.

Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India



Mylan[®] | Mylan.com

RMX2351C

NDC 0378-2351-10

**Esomeprazole
Magnesium
Delayed-release
Capsules, USP**

40 mg*



PHARMACIST: Dispense the Medication Guide provided separately to each patient.

 **Mylan**[®]

Rx only

1000 Capsules



Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

**NO VARNISH
ZONE**





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.

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

RECENT MAJOR CHANGES	
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
Warnings and Precautions, Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.10)	03/2014

INDICATIONS AND USAGE
Esomeprazole magnesium delayed-release capsules, USP are 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)

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Adults	20 mg or 40 mg	Once daily for 4 to 8 weeks
12 to 17 Years	20 mg or 40 mg	Once daily for up to 8 weeks
1 to 11 Years	10 mg or 20 mg	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
Pathological Hypersecretory Conditions		
	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 therapy. (5.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 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 may be considered. **Maintenance of Healing of Erosive Esophagitis:** Esomeprazole magnesium delayed-release capsules 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 are indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children one year of older.
1.2 Risk Reduction of NSAID-associated Gastric Ulcer
Esomeprazole magnesium delayed-release capsules are indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (≥ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.
1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Esomeprazole magnesium delayed-release capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

2 DOSE AND ADMINISTRATION
Esomeprazole magnesium is supplied as delayed-release capsules for oral administration. The recommended doses are outlined in Table 1. Esomeprazole magnesium delayed-release capsules 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 Magnesium Delayed-release Capsules	Indication	Recommended Dosage	Frequency
Gastroesophageal Reflux Disease (GERD)			
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*	
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily**	
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks**	
Pediatric GERD			
12 to 17 Year Olds			
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks	
Symptomatic GERD	20 mg	Once Daily for 4 Weeks	
1 to 11 Year Olds*			
Short-term Treatment of Symptomatic GERD	10 mg	Once Daily for up to 8 Weeks	
Healing of Erosive Esophagitis			
Weight < 20 kg	10 mg	Once Daily for 8 Weeks	
Weight ≥ 20 kg	10 mg or 20 mg	Once Daily for 8 Weeks	
Risk Reduction of NSAID-associated Gastric Ulcer			
	20 mg or 40 mg	Once Daily for up to 6 Months**	
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome			
	40 mg†	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 6 months.
*** If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.
† Doses over 1 mg/kg/day have not been studied.
‡ The dosage of esomeprazole 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)].

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 20 mg of esomeprazole should not be exceeded [see Clinical Pharmacology (12.3)].
Directions for use specific to the route and available methods of administration for this dosage form are presented in Table 2.

Table 2: Administration Options	Administration Options	
Dosage Form	Route	Options
Delayed-release Capsules	Oral	Capsule can be swallowed whole.
		-or- Capsule can be opened and mixed with applesauce.
Delayed-release Capsules	Nasogastric Tube	Capsule can be opened and the intact pellets emptied into a syringe and delivered through the nasogastric tube.

Esomeprazole Magnesium Delayed-release Capsules: Esomeprazole magnesium delayed-release capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the esomeprazole magnesium delayed-release capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets 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 pellets should not be chewed or crushed. If the pellets/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 pellets emptied into a 60 mL catheter tipped syringe and mixed with 50 mL of water. It is important to only use a catheter tipped syringe when administering esomeprazole through a nasogastric tube. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for pellets remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the pellets, the nasogastric tube should be flushed with additional water. Do not administer the pellets if they have dissolved or disintegrated.

The mixture must be used immediately after preparation.

3 DOSE FORMS AND STRENGTHS
• The 20 mg capsule is a hard-shell gelatin capsule with a white opaque cap and white opaque body filled with white to off-white colored pellets. The capsule is axially printed with **M150** in black ink on the cap and body.
• The 40 mg capsule is a hard-shell gelatin capsule with a white opaque cap and white opaque body filled with white to off-white colored pellets. The capsule is axially printed with **M151** in black ink on the cap and body.

4 CONTRAINDICATIONS
Esomeprazole magnesium delayed-release capsules are contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [see Adverse Reactions (6)].

5 WARNINGS AND PRECAUTIONS
5.1 Concurrent Gastric Malignancy
Symptomatic response to therapy with esomeprazole does not preclude the presence of gastric malignancy.

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

- 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) may lead to malabsorption or a deficiency of cyanocobalamin. (5.4)
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea. (5.5)
- Avoid concomitant use of esomeprazole 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 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 (≥ 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

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended; if saquinavir is used with esomeprazole, 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, digoxin and mycophenolate mofetil). Patients treated with esomeprazole and digoxin may need to be monitored for digoxin toxicity. (7.2)
• Combined inhibitor of CYP2C19 and 3A4 may raise esomeprazole levels. (7.3)
• Clopidogrel: Esomeprazole decreases exposure to the active metabolite of clopidogrel. (7.3)
• May increase systemic exposure of citalostazol and an active metabolite. Consider dose reduction. (7.3)
• Tacrolimus: Esomeprazole may increase serum levels of tacrolimus (7.5)
• Methotrexate: Esomeprazole may increase serum levels of methotrexate. (7.7)

USE IN SPECIFIC POPULATIONS
• Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

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MX:ESOME:R2mh;MX:MG:ESOME:R2mh

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

5.3 Acute Interstitial Nephritis

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

5.4 Cyanocobalamin (Vitamin B-12) Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Patients should be monitored for cyanocobalamin deficiency occurring with acid-suppressing therapy as reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

5.5 *Clostridium difficile* Associated Diarrhea
Published observational studies suggest that PPI therapy like esomeprazole 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.

5.6 Interaction with Clopidogrel
Avoid concomitant use of esomeprazole 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 may 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 consider alternative anti-platelet therapy [see Drug Interactions (7.3) and Pharmacokinetics (12.3)].

5.7 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)].

5.8 Hypomagnesemia
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 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), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions (6.2)].

5.9 Concomitant Use of Esomeprazole with St. John's Wort or Rifampin
Drugs which induce CYP2C19 or CYP3A4 (such as St. John's wort or rifampin) can substantially decrease esomeprazole concentrations [see Drug Interactions (7.3)]. Avoid concomitant use of esomeprazole with St. John's wort or rifampin.

5.10 Interactions with Diagnostic Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels are used secondary to drug-induced decreases in gastric acidity. The increased CgA level, which included 1240 patients on esomeprazole 20 mg, 4,234 patients on esomeprazole 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions (≥ 1%) in all three groups were headache (5.5, 5.4, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole or omeprazole.
Additional adverse reactions that were reported as possibly or probably related to esomeprazole with an incidence < 1% are listed below by body system:
Body as a Whole: abnormal enlarged, allergic reaction, asthma, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flashes, 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;
Headache: earache, tinnitus;
Hematology: anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia;
Hepatic: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased;
Melanin/Nutritional: glycosuria, hyperuricemia, hypotatemia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease;
Musculoskeletal: arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polyomyelitis rheumatica;
Nervous System/Psychiatric: anorexia, anorexia, appetite increased, confusion, depression aggravated, dizziness, hypertension, nervousness, hyposthesia, 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, urticaria, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria;
Special Senses: otitis media, parosmia, taste loss, taste perversion;
Urogenital: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria;
Visual: conjunctivitis, vision abnormal.

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole, were reported in ≥ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone [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.

Adults: The safety of esomeprazole 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 to 12 months. In general, esomeprazole 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 controlled clinical trials, which included 1240 patients on esomeprazole 20 mg, 4,234 patients on esomeprazole 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions (≥ 1%) in all three groups were headache (5.5, 5.4, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole or omeprazole.

Additional adverse reactions that were reported as possibly or probably related to esomeprazole with an incidence < 1% are listed below by body system:
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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;
Headache: earache, tinnitus;
Hematology: anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia;
Hepatic: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased;
Melanin/Nutritional: glycosuria, hyperuricemia, hypotatemia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease;
Musculoskeletal: arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polyomyelitis rheumatica;
Nervous System/Psychiatric: anorexia, anorexia, appetite increased, confusion, depression aggravated, dizziness, hypertension, nervousness, hyposthesia, 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, urticaria, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria;
Special Senses: otitis media, parosmia, taste loss, taste perversion;
Urogenital: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria;
Visual: conjunctivitis, vision abnormal.

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole, were reported in ≥ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone [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 were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Pediatrics: The safety of esomeprazole was evaluated in 316 pediatric and adolescent patients aged 1

to 17 years in four clinical trials for the treatment of symptomatic GERD [see Clinical Studies (14.2)]. In 109 pediatric patients aged 1 to 11 years, the most frequently reported (at least 1%) treatment-related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17 years the most frequently reported (at least 2%) treatment-related adverse reactions in these patients were headache (8.1%), abdominal pain (2.7%), diarrhea (2%), and nausea (2%).

No new safety concerns were identified in pediatric patients.
6.2 Post-marketing Experience
The following adverse reactions have been identified during post-approval use of esomeprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:
Blood And Lymphatic: agranulocytosis, pancytopenia;
Eye: blurred vision;
Gastrointestinal: pancreatitis, stomatitis; microscopic colitis;
Hepatic/Biliary: 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, with or without hypocalcemia and/or hypokalemia;
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: gynecostasia;
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. Co-administration of atazanavir and nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction.
Renal and Urinary: interstitial nephritis;
Reproductive System and Breast: gynecostasia;
Respiratory, Thoracic, and Mediastinal: bronchospasm;
Skin and Subcutaneous Tissue: alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

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 38% and 32%, C_{max} by 37% and 32%, and C_{2h} by 39% and 37%, respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{2h} 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_{2h} by 105% following multiple dosing of saquinavir/trifluoracetate (1100 mg/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered 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.

There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

7.2 Drugs for Which Gastric pH Can Affect Bioavailability
Due to its effects on gastric acid secretion, esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole.

Esomeprazole is an enantiomer of omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Co-administration 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.

Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution in transplant patients receiving MMF [see Clinical Pharmacology (12

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 four 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 healthy 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* (7)].

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.

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.

12.4 Microbiology

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 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 carcinomas 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 carcinomas 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 3.4 times the human dose of 40 mg/day on a body surface area basis) for one year, then followed for an additional year without the drug. No carcinomas were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one 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 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, 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 on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole 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 42 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 at doses of 70 to 280 mg/kg/day (about 17 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 from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 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 length 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 40 mg, esomeprazole 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 20 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
	654	Esomeprazole 40 mg	75.9%	94.1%	
2	656	Esomeprazole 20 mg	70.5%	89.9%	p < 0.05
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	Esomeprazole 40 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1,216	Esomeprazole 40 mg	81.7%	93.7%	p < 0.001
	1,209	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 the Table 8:

Table 8: Sustained Resolution¹ of Heartburn (Erosive Esophagitis Patients)

Study	No. of Patients	Treatment Groups	Cumulative Percent ² with Sustained Resolution		Significance Level*
			Day 14	Day 28	
1	573	Esomeprazole 20 mg	64.3%	72.7%	N.S.
	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	Esomeprazole 40 mg	64.8%	74.2%	p < 0.001
	620	Esomeprazole 20 mg	62.9%	70.1%	
3	568	Esomeprazole 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1,187	Esomeprazole 40 mg	67.6%	75.1%	p < 0.001
	1,188	Omeprazole 20 mg	62.5%	70.8%	

¹ Defined as 7 consecutive days with no heartburn reported in daily patient diary.

² 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 40 mg, 7 to 8 days for esomeprazole 20 mg and 7 to 9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of esomeprazole 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 four-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate esomeprazole 40 mg (N = 174), 20 mg (N = 180), 10 mg (N = 168) or placebo (N = 171) once daily over 6 months of treatment.

No additional clinical benefit was seen with esomeprazole 40 mg over esomeprazole 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)

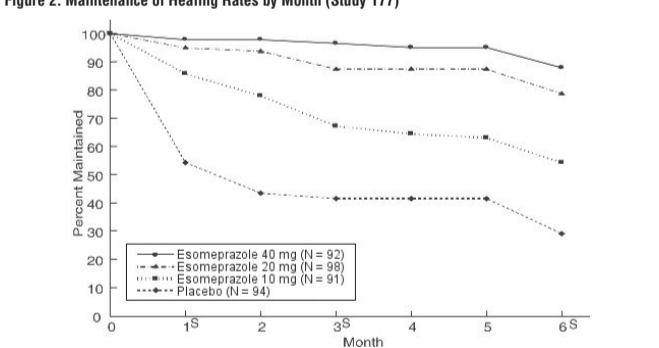
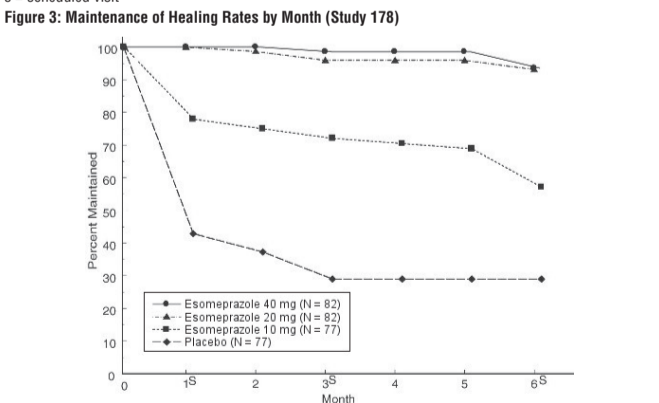


Figure 3: Maintenance of Healing Rates by Month (Study 178)



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 compared to placebo.

In both studies, the proportion of patients on esomeprazole 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 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for 6 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 4 weeks of treatment with esomeprazole 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 4 of the 7 days immediately preceding randomization.

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

No additional clinical benefit was seen with esomeprazole 40 mg over esomeprazole 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)

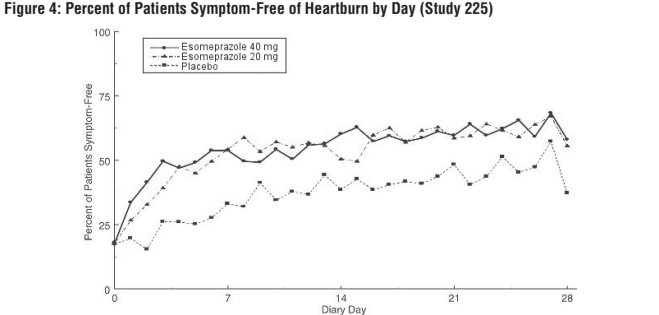
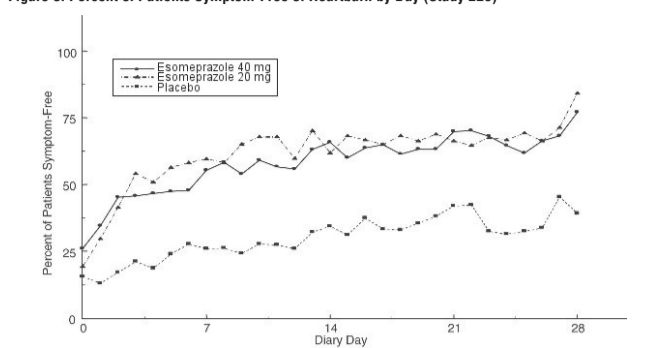


Figure 5: Percent of Patients Symptom-Free of Heartburn by Day (Study 226)



In three European symptomatic GERD trials, esomeprazole 20 mg and 40 mg and omeprazole 20 mg were evaluated. No significant treatment-related differences were seen.

14.3 Pediatric Gastroesophageal Reflux Disease (GERD)

One to 11 Years of Age: In a multicenter, parallel-group study, 109 pediatric patients with a history of endoscopically-proven GERD (1 to 11 years of age; 53 female; 89 Caucasian, 19 Black, 1 Other) were treated with esomeprazole once daily for up to 8 weeks to evaluate safety and tolerability. Dosing by patient weight was as follows:

- weight < 20 kg: once daily treatment with esomeprazole 5 mg or 10 mg
- weight > 20 kg: once daily treatment with esomeprazole 10 mg or 20 mg

Patients were endoscopically characterized as to the presence or absence of erosive esophagitis. Of the 109 patients, 53 had erosive esophagitis at baseline (51 had mild, 1 moderate, and 1 severe esophagitis). Although most of the patients who had a follow-up endoscopy at the end of 8 weeks of treatment healed, spontaneous healing cannot be ruled out because these patients had low grade erosive esophagitis prior to treatment, and the trial did not include a concomitant control.

12 to 17 Years of Age: In a multicenter, randomized, double-blind, parallel-group study, 149 adolescent patients (12 to 17 years of age; 89 female; 124 Caucasian, 15 Black, 10 Other) with clinically diagnosed GERD were treated with either esomeprazole 20 mg or esomeprazole 40 mg once daily for up to 8 weeks to evaluate safety and tolerability. Patients were not endoscopically characterized as to the presence or absence of erosive esophagitis.

14.4 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 1,429 patients were randomized across the two studies. Patients ranged in age from 19 to 89 (median age 66 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 esomeprazole 20 mg or 40 mg once a day experienced significant reduction in gastric ulcer occurrences relative to placebo treatment at 26 weeks. See Table 9. No additional benefit was seen with esomeprazole 40 mg over esomeprazole 20 mg. These studies did not demonstrate significant reduction in the development of NSAID-associated duodenal ulcer due to the low incidence.

Table 9: Cumulative Percentage of Patients without Gastric Ulcers at 26 Weeks:

Study	No. of Patients	Treatment Groups	% of Patients Remaining Gastric Ulcer Free ¹
1	191	Esomeprazole 20 mg	95.4
	194	Esomeprazole 40 mg	96.7
	184	Placebo	88.2
2	267	Esomeprazole 20 mg	94.7
	271	Esomeprazole 40 mg	95.3
	257	Placebo	83.3

¹ % = Life Table Estimate. Significant difference from placebo (p < 0.01).

14.6 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 3 Black, mean age of 55.5 years) with pathological hypersecretory conditions, such as Zollinger-Ellison Syndrome, esomeprazole significantly inhibited gastric acid secretion. Initial dose was 40 mg twice daily in 19/21 patients and 80 mg twice daily in 2/21 patients. Total daily doses ranging from 80 mg to 240 mg 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/h 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/h). Of the 19 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 Dose at the Month 12 Visit	BAO Under Adequate Control at the Month 12 Visit (N = 20)*
40 mg twice daily	13/15
80 mg twice daily	4/4
80 mg three times daily	1/1

* One patient was not evaluated.

16 HOW SUPPLIED/STORAGE AND HANDLING

Esomeprazole Magnesium Delayed-release Capsules, USP are available containing 22.25 mg or 44.50 mg of esomeprazole magnesium, USP equivalent to 20 mg or 40 mg of esomeprazole, respectively. The 20 mg capsule is a hard-shell gelatin capsule with a white opaque cap and white opaque body filled with white to off-white colored pellets. The capsule is axially printed with **M150** in black ink on the cap and body. They are available as follows:

NDC 0378-2350-93

bottles of 30 capsules

NDC 0378-2350-10

bottles of 1000 capsules

The 40 mg capsule is a hard-shell gelatin capsule with a white opaque cap and white opaque body filled with white to off-white colored pellets. The capsule is axially printed with **M151** in black ink on the cap and body. They are available as follows:

NDC 0378-2351-93

bottles of 30 capsules

NDC 0378-2351-10

bottles of 1000 capsules

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

17 PATIENT COUNSELING INFORMATION

"See FDA-approved Medication Guide"

- Advise patients to let you know if they are taking, or begin taking, other medications, because esomeprazole can interfere with antiretroviral drugs and drugs that are affected by gastric pH changes [see *Drug Interactions* (7.1)].
- Let patients know that antacids may be used while taking esomeprazole magnesium delayed-release capsules.
- Advise patients to take esomeprazole magnesium delayed-release capsules at least one hour before a meal.
- For patients who are prescribed esomeprazole magnesium delayed-release capsules, advise them not to chew or crush the capsules.
- Advise patients that, if they open esomeprazole magnesium delayed-release capsules to mix the pellets with food, the pellets 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 magnesium 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. Instruct patients to rinse the syringe with water after each use.

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* (5.5)].

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* (5.8)].

MEDICATION GUIDE ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES, USP (es' oh mep' ra zole mag nee' zee um) 20 mg and 40 mg

Read the Medication Guide that comes with esomeprazole magnesium delayed-release capsules before you start taking esomeprazole magnesium delayed-release capsules 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 magnesium delayed-release capsules?

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

Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:

- Diarrhea.** Esomeprazole magnesium delayed-release capsules 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 magnesium delayed-release capsules 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 magnesium delayed-release capsules.

Esomeprazole magnesium delayed-release capsules can have other serious side effects. See "What are the possible side effects of esomeprazole magnesium delayed-release capsules?"

What are esomeprazole magnesium delayed-release capsules?

Esomeprazole magnesium delayed-release capsules are a prescription medicine called a proton pump inhibitor (PPI). Esomeprazole magnesium delayed-release capsules reduce the amount of acid in your stomach.

Esomeprazole magnesium delayed-release capsules are used in adults:

- for 4 to 8 weeks to treat the symptoms of gastroesophageal reflux disease (GERD). Esomeprazole magnesium delayed-release capsules 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).
- 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.

For children and adolescents 1 year to 17 years of age, esomeprazole magnesium delayed-release capsules may be prescribed for up to 8 weeks for short-term treatment of GERD.

Who should not take esomeprazole magnesium delayed-release capsules?

Do not take esomeprazole magnesium delayed-release capsules if you:

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

What should I tell my doctor before taking esomeprazole magnesium delayed-release capsules?

Before you take esomeprazole magnesium delayed-release capsules, tell your doctor if you:

- have been told that you have low magnesium levels in your blood
- have liver problems
- are pregnant or plan to become pregnant. It is not known if esomeprazole can harm your unborn baby.
- are breastfeeding or planning to breastfeed. Esomeprazole may pass into your breastmilk. Talk to your doctor about the best way to feed your baby if you take esomeprazole magnesium delayed-release capsules.

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

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)
- mycophenolate mofetil (Cellcept)

How should I take esomeprazole magnesium delayed-release capsules?

- Take esomeprazole magnesium delayed-release capsules exactly as prescribed by your doctor.
- Do not change your dose or stop esomeprazole without talking to your doctor.
- Take esomeprazole magnesium delayed-release capsules at least one hour before a meal.
- Swallow esomeprazole magnesium delayed-release capsules whole. **Never chew or crush esomeprazole magnesium delayed-release capsules.**
- If you have difficulty swallowing esomeprazole magnesium delayed-release capsules, you may open the capsule and empty the contents into a tablespoon of applesauce. Do not crush or chew the pellets. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you forget to take a dose of esomeprazole, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.
- If you take too much esomeprazole, 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 how to mix and give esomeprazole magnesium delayed-release capsules through a nasogastric tube or gastric tube.

What are the possible side effects of esomeprazole magnesium delayed-release capsules?

Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:

- See "What is the most important information I should know about esomeprazole magnesium delayed-release capsules?"**
- Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis).** Using esomeprazole magnesium delayed-release capsules 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.
- Vitamin B-12 deficiency.** Esomeprazole magnesium delayed-release capsules reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor about the possibility of vitamin B-12 deficiency if you have been on esomeprazole magnesium delayed-release capsules for a long time (more than 3 years).
- Low magnesium levels in your body.** 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 magnesium delayed-release capsules or during treatment if you will be taking esomeprazole magnesium delayed-release capsules for a long period of time.

The most common side effects with esomeprazole magnesium delayed-release capsules may include:

- headache
- diarrhea
- nausea
- gas
- abdominal pain
- constipation
- dry mouth
- drowsiness

Other side effects:

MEDICATION GUIDE

ESOMEPRAZOLE MAGNESIUM DELAYED-RELEASE CAPSULES, USP

(es" oh mep' ra zole mag nee' zee um)

20 mg and 40 mg

Read the Medication Guide that comes with esomeprazole magnesium delayed-release capsules before you start taking esomeprazole magnesium delayed-release capsules 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 magnesium delayed-release capsules?

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

Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:

- **Diarrhea.** Esomeprazole magnesium delayed-release capsules 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 magnesium delayed-release capsules 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 magnesium delayed-release capsules. Esomeprazole magnesium delayed-release capsules can have other serious side effects. See **"What are the possible side effects of esomeprazole magnesium delayed-release capsules?"**

What are esomeprazole magnesium delayed-release capsules?

Esomeprazole magnesium delayed-release capsules are a prescription medicine called a proton pump inhibitor (PPI). Esomeprazole magnesium delayed-release capsules reduce the amount of acid in your stomach.

Esomeprazole magnesium delayed-release capsules are used in adults:

- for 4 to 8 weeks to treat the symptoms of gastroesophageal reflux disease (GERD). Esomeprazole magnesium delayed-release capsules 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).
- 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.

For children and adolescents 1 year to 17 years of age, esomeprazole magnesium delayed-release capsules may be prescribed for up to 8 weeks for short-term treatment of GERD.

Who should not take esomeprazole magnesium delayed-release capsules?

Do not take esomeprazole magnesium delayed-release capsules if you:

- are allergic to esomeprazole magnesium or any of the ingredients in esomeprazole magnesium delayed-release capsules. See the end of this Medication Guide for a complete list of ingredients in esomeprazole magnesium delayed-release

capsules.

- are allergic to any other Proton Pump Inhibitor (PPI) medicine.

What should I tell my doctor before taking esomeprazole magnesium delayed-release capsules?

Before you take esomeprazole magnesium delayed-release capsules, tell your doctor if you:

- have been told that you have low magnesium levels in your blood
- have liver problems
- are pregnant or plan to become pregnant. It is not known if esomeprazole can harm your unborn baby.
- are breastfeeding or planning to breastfeed. Esomeprazole may pass into your breastmilk. Talk to your doctor about the best way to feed your baby if you take esomeprazole magnesium delayed-release capsules.

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

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)
- mycophenolate mofetil (Cellcept)

How should I take esomeprazole magnesium delayed-release capsules?

- Take esomeprazole magnesium delayed-release capsules exactly as prescribed by your doctor.
- Do not change your dose or stop esomeprazole without talking to your doctor.
- Take esomeprazole magnesium delayed-release capsules at least one hour before a meal.
- Swallow esomeprazole magnesium delayed-release capsules whole. **Never chew or crush esomeprazole magnesium delayed-release capsules.**
- If you have difficulty swallowing esomeprazole magnesium delayed-release capsules, you may open the capsule and empty the contents into a tablespoon of applesauce. Do not crush or chew the pellets. Be sure to swallow the applesauce right away. Do not store it for later use.
- If you forget to take a dose of esomeprazole, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take a double dose to make up for a missed dose.
- If you take too much esomeprazole, 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 how to mix and give esomeprazole magnesium delayed-release capsules through a nasogastric tube or gastric tube.

What are the possible side effects of esomeprazole magnesium delayed-release capsules?

Esomeprazole magnesium delayed-release capsules can cause serious side effects, including:

- **See "What is the most important information I should know about esomeprazole magnesium delayed-release capsules?"**
- **Chronic (lasting a long time) inflammation of the stomach lining (Atrophic Gastritis).** Using esomeprazole magnesium delayed-release capsules 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.
- **Vitamin B-12 deficiency.** Esomeprazole magnesium delayed-release capsules reduce the amount of acid in your stomach. Stomach acid is needed to absorb vitamin B-12 properly. Talk with your doctor about the possibility of vitamin B-12 deficiency if you have been on esomeprazole magnesium delayed-release capsules for a long time (more than 3 years).
- **Low magnesium levels in your body.** 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 magnesium delayed-release capsules or during treatment if you will be taking esomeprazole magnesium delayed-release capsules for a long period of time.

The most common side effects with esomeprazole magnesium delayed-release capsules may include:

- headache
- diarrhea
- nausea
- gas
- abdominal pain
- constipation
- dry mouth
- drowsiness

Other side effects:

Serious allergic reactions. Tell your doctor if you get any of the following symptoms with esomeprazole magnesium delayed-release capsules:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop esomeprazole magnesium delayed-release capsules 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 magnesium delayed-release capsules.

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 magnesium delayed-release capsules?

- Store esomeprazole magnesium delayed-release capsules at 20° to 25°C (68° to 77°F).
- Keep the container of esomeprazole magnesium delayed-release capsules closed tightly.

Keep esomeprazole magnesium delayed-release capsules and all medicines out of the reach of children.

General Information About Esomeprazole Magnesium Delayed-release Capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use esomeprazole for a condition for which it was not prescribed. Do not give esomeprazole 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 magnesium delayed-release capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about esomeprazole magnesium delayed-release capsules that is written for health professionals.

For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in esomeprazole magnesium delayed-release capsules?

Active Ingredient: esomeprazole magnesium, USP

Inactive Ingredients in Esomeprazole Magnesium Delayed-release Capsules (including the capsule shells): crospovidone, hydroxypropyl cellulose, mannitol, methacrylic acid copolymer type C, sucrose, sugar spheres, talc, titanium dioxide and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin and titanium dioxide. The imprinting ink contains black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

Instructions for Use

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

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

Esomeprazole Magnesium Delayed-release Capsules:

- Open the capsule and empty the pellets into a 60 mL catheter tipped syringe. Mix with 50 mL of water. Use only a catheter tipped syringe to give esomeprazole 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 pellets in the tip.
- Give the medicine right away.
- Do not give the pellets 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 pellets, flush the NG tube with more water.

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

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