PRODUCT MONOGRAPH

PrMYLAN-ESOMEPRAZOLE

Esomeprazole Delayed Release Tablets

20 mg and 40 mg esomeprazole (as esomeprazole magnesium trihydrate)

H^+, K^+-ATPase Inhibitor

Mylan Pharmaceuticals ULC 85 Advance Rd. Etobicoke, Ontario Canada M8Z 2S6 Control Number: 212758	Date of Revision: February 9, 2018

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[Pr]MYLAN-ESOMEPRAZOLE

Esomeprazole Delayed Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	tablet / 20 mg and 40 mg esomeprazole	Cellulose microcrystalline, crospovidone, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, iron oxide, magnesium stearate, methacrylic acid ethylacrylate copolymer, polyethylene glycol, polysorbate, synthetic paraffin, sodium stearyl fumarate, sugar spheres, talc, titanium dioxide and triethyl citrate

INDICATIONS AND CLINICAL USE

Adults

MYLAN-ESOMEPRAZOLE (esomeprazole delayed release tablets) is indicated for treatment of conditions where a reduction in gastric acid secretion is required such as:

- reflux esophagitis
- maintenance treatment of patients with reflux esophagitis
- nonerosive reflux disease (NERD) (i.e. heartburn and regurgitation)
- healing of NSAID*-associated gastric ulcers
- reduction of risk of NSAID-associated gastric ulcers
- treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome
- *Helicobacter pylori* (*H. pylori*) eradication

MYLAN-ESOMEPRAZOLE, in combination with clarithromycin and amoxicillin, is indicated for the treatment of patients with duodenal ulcer disease associated with *Helicobacter pylori* infection to eradicate the *H. pylori* and heal ulcers. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

*Note: Superiority of esomeprazole delayed release tablets over ranitidine 150 mg BID with the use of non-selective NSAIDs was demonstrated. Superiority was not established with the use of COX-2 selective NSAIDs alone due to the small number of patients analysed in this subgroup (See Table 10 in the Clinical Trial section)

Pediatrics (1-17 years of age)

MYLAN-ESOMEPRAZOLE (esomeprazole delayed release tablets) is indicated for treatment of conditions where a reduction in gastric acid secretion is required such as:

- reflux esophagitis
- nonerosive reflux disease (NERD) (i.e. heartburn and regurgitation)

CONTRAINDICATIONS

- Hypersensitivity to esomeprazole, substituted benzimidazoles or any of the components of this medication (see Dosage Forms, Composition and Packaging).
- When used for eradication of *Helicobacter pylori*, the contraindications for amoxicillin and clarithromycin as found in the corresponding Product Monographs should be taken into consideration.
- Co-administration with rilprivirine is contraindicated.

WARNINGS AND PRECAUTIONS

General

In the presence of any alarm symptom (*e.g.*, significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melena), and/or when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Antibiotic Combination Therapy:

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, which are used together with PPIs for the treatment of *H. pylori*, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

***Clostridium Difficile* Associated Diarrhea:**

Decreased gastric acidity due to any means, including any proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors can lead to an increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

An increased risk for *Clostridium difficile* infection (CDI) and *Clostridium difficile* associated diarrhea (CDAD) has been observed in association with PPI use in several observational studies. CDI/CDAD should be considered in the differential diagnosis for diarrhea that does not improve. Additional risk factors for CDI and CDAD include recent hospitalization, the use of antibiotics, old age and the presence of comorbidities.

Patients should be prescribed PPIs at the lowest dose and for the shortest duration required for the condition being treated and be reassessed to ascertain whether continued PPI therapy remains beneficial.

Concomitant use of clopidogrel:

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75mg daily maintenance dose) and esomeprazole (40 mg once daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided (see DRUG INTERACTIONS).

Concomitant use of Proton Pump Inhibitors (PPIs) with Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate

toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate (see DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

Long-term toxicity studies of omeprazole, revealed the gastric mucosa as the target organ. The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In the rat carcinogenicity study (24 months), ECL-cell carcinoids were found in some animals treated with 14-140 mg/kg/day for their normal life span. ECL-cell carcinoids were seen in a background of ECL-cell hyperplasia. No ECL-cell carcinoids were identified in the carcinogenicity study in mice or in long-term (up to 7 years) general toxicity studies in dogs.

A vast number of studies have revealed that pronounced and sustained hypergastrinemia is the mechanism behind the development of the gastric ECL-cell carcinoids in the rat. Such ECL carcinoids have been seen in rats after life-long treatment with other inhibitors of acid secretion such as H2-receptor blockers and other proton pump inhibitors. Partial fundectomy in rats results in hypergastrinemia and gastric ECL-cell carcinoids in the remaining part of the fundic mucosa, towards the end of the rats' life span.

Treatment with esomeprazole delayed release tablets for up to 1 year in more than 800 patients has not resulted in any significant pathological changes in the gastric oxyntic endocrine cells. Short-term treatment and long-term treatment with the racemate, omeprazole, capsules in a limited number of patients for up to 11 years have not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

During treatment with all antisecretory drugs serum gastrin increases in response to the decreasedacid secretion. The effect of esomeprazole delayed release tablets 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 6-12 months (daily doses of either 20 or 40 mg). The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau (approximately 100 pg/mL) within two to three months of therapy and returned to baseline levels (approximately 30-40 pg/mL) within four weeks after discontinuation of therapy.

Drug Interactions with Antiretroviral Drugs
PPIs have been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible mechanisms are via CYP 2C19.

Rilpivirine:

Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS).

Atazanavir and Nelfinavir:

Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the REYATAZ AND VIRACEPT Product Monographs).
If the combination of MYLAN-ESOMEPRAZOLE with atazanavir is judged unavoidable, close clinical monitoring is recommended in combination with the use of 400 mg atazanavir/100 mg ritonavir dose; the dose of MYLAN-ESOMEPRAZOLE should not exceed an equivalent dose omeprazole of 20 mg daily (see REYATAZ Product Monograph).

Saquinavir:

If MYLAN-ESOMEPRAZOLE is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities, including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation are recommended. Dose reduction of saquinavir should be considered from the safety perspective for individual patients (see INVIRASE Product Monograph).

Endocrine and Metabolism

Hypomagnesaemia, Hypokalemia and Hypocalcemia: The chronic use of PPIs may lead to hypomagnesaemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Cyanocobalamin (Vitamin B12) Deficiency: The prolonged use of PPIs, may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (Vitamin B12) deficiency.

Immune

Subacute cutaneous lupus erythematosus:
Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping MYLAN-ESOMEPRAZOLE. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Interference with Laboratory Tests

During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, MYLAN-ESOMEPRAZOLE treatment should be stopped 14 days before CgA measurements (see DRUG INTERACTIONS).

Musculoskeletal and Connective Tissue

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 and ADVERSE REACTIONS).

Special Populations

Pregnant Women: The safety of esomeprazole magnesium in pregnancy has not been established. Esomeprazole delayed release tablets should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Women: It has not been investigated whether or not esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore, esomeprazole delayed release tablets should not be given to nursing mothers unless its use is considered essential.

Pediatrics (1-17 years of age): The use of esomeprazole magnesium in pediatric patients (1 to 17 years of age) for the short term treatment (up to 8 weeks) of GERD is supported by extrapolation of results already included in the currently approved labelling from a) adequate and well-controlled studies in adults that supported the approval of esomeprazole delayed release tablets for adults, and additionally from b) safety and pharmacokinetic studies performed in pediatric patients (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pediatrics (1-17 years of age), ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Pediatrics (1-17 years of age) and CLINICAL TRIALS, In Pediatrics (1-17 years of age)).

No data is currently available in children (1-11 years of age) with hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

The safety and effectiveness of esomeprazole delayed release tablets have not yet been established in pediatric patients <1 years of age.

Geriatrics (> 71 years of age): The metabolism of esomeprazole magnesium is not significantly changed in elderly subjects. Following repeated oral dosing with 40 mg esomeprazole delayed release tablets in healthy elderly subjects (6 males, 8 females; 71 to 80 years of age), AUC and C_{max} values measured were similar to those previously measured in young GERD patients (ratio of AUC values in elderly vs. GERD subjects: 1.25; ratio of C_{max} values: 1.18). Therefore, dose adjustment is not required in the elderly.

Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category may already be at high risk for osteoporosis-related fractures. If the use of PPIs is

required, they should be managed carefully according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

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 metabolism of esomeprazole magnesium in patients with mild to moderate liver dysfunction (Child Pugh Class A or B), is similar to that in patients with symptoms of GERD with normal liver function. Metabolism of esomeprazole is decreased in patients with severe liver dysfunction (Child Pugh Class C) resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. The plasma elimination half-life in patients with severe liver dysfunction is still very short (3 hours) relative to the dosing interval (24 hours). Esomeprazole and its major metabolites do not show any tendency to accumulate with once-daily dosing. Dose adjustment is not required in patients with mild to moderate liver impairment. A daily dose of 20 mg in patients with severe liver disease should not, as a rule, be exceeded (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Since the kidney is responsible for the excretion of metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function. Esomeprazole is extensively protein-bound and is, therefore, not expected to be readily dialyzable. Dose adjustment is not required in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Poor Metabolizers: The CYP 2C19 and CYP 3A4 isozymes are responsible for metabolism of esomeprazole. CYP 2C19, which is involved in the metabolism of all available proton pump inhibitors, exhibits polymorphism. Approximately 3% of Caucasians and 15-20% of Asians lack CYP 2C19 and are termed "poor metabolizers". At steady state, the ratio of AUC in poor metabolizers to AUC in the rest of the population is approximately 2. Dosage adjustment of esomeprazole magnesium based on CYP 2C19 status is not necessary.

Monitoring and Laboratory Tests

The clinical documentation for esomeprazole delayed release tablets does not support the need for routine laboratory monitoring of response to therapy. (See WARNINGS and PRECAUTIONS – Carcinogenesis and Mutagenesis for effects of esomeprazole magnesium on serum gastrin levels and ADVERSE REACTIONS – Post-Market Adverse Drug Reactions for effects on liver functioning).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Esomeprazole magnesium is well-tolerated. Most adverse reactions have been mild and transient, showing no consistent relationship with treatment.

Adverse reactions have been recorded during controlled clinical investigations in >8500 adult patients exposed to esomeprazole magnesium. Additionally >1200 adult subjects/patients were exposed to esomeprazole magnesium in Phase I studies. Among reactions which occurred with a frequency of >1% in clinical studies, only headache, diarrhea, flatulence, abdominal pain, nausea, vomiting, dizziness and dry mouth are thought to be associated with the use of esomeprazole magnesium.

Adverse reactions have been recorded during a clinical investigation in 109 pediatric patients (1-11 years of age) exposed to esomeprazole magnesium. Among reactions which occurred with a frequency of >1% in clinical studies, only diarrhea, headache and somnolence are associated with the use of esomeprazole magnesium. No new safety concerns were identified. Adverse reactions have also been recorded during a clinical investigation in 149 pediatric patients (12-17 years of age) exposed to esomeprazole magnesium. The treatment related adverse event profile was found to be consistent with that seen in adults.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults

The following adverse reactions, irrespective of causal relationship, were reported (at a rate of more than 1%) in controlled short-term (up to 8 weeks) clinical trials involving 5668 patients:

Table 1 Percentage of Patients Reporting Adverse Reactions, Irrespective of Causal Relationship, (at a Rate of More than 1%) in Short Term Clinical Trials (Up to 8 weeks) Treated With Esomeprazole delayed release tablets.

Adverse Reaction	All studies	Placebo controlled studies	
	Esomeprazole DR tablets (20 & 40 mg) n = 5668 (%)	Esomeprazole DR tablets (20 & 40 mg) n = 470 (%)	Placebo n = 240 (%)
Body as a Whole			
Headache	8.4	6.6	7.5
Gastrointestinal			
Diarrhea	5.7	5.7	4.2
Abdominal Pain	3.6	5.7	2.5
Nausea	3.5	5.1	5.4
Flatulence	3.3	3.2	-

Adverse Reaction	All studies	Placebo controlled studies	
	Esomeprazole DR tablets (20 & 40 mg) n = 5668 (%)	**Esomeprazole DR tablets (20 & 40 mg) n = 470 (%)**	**Placebo n = 240 (%)**
Gastritis	2.1	-	-
Constipation	1.6	1.7	1.3
Vomiting	1.4	1.1	1.7
Mouth dry	1.3	1.3	-
Respiratory			
Respiratory infection	3.8	1.9	3.8
Sinusitis	1.7	2.8	2.5
Pharyngitis	1.3	0.4	1.3
Nervous System			
Dizziness	1.2	0.9	1.7
Resistance Mechanism			
Viral infection	1.1	-	0.4

In clinical trials up to 6 months' duration, the following adverse reactions were reported.

Table 2 Percentage of Patients Reporting Adverse Reactions, Irrespective of Causal Relationship, (at a Rate of More than 3%) in Clinical Trials Up to 6 Months' Duration Treated with Esomeprazole delayed release tablets.

Adverse Reaction	Esomeprazole DR tablets (10, 20 & 40 mg) n = 519 (%)	Placebo n = 169 (%)
Body as a Whole		
Headache	6.6	4.1
Gastrointestinal		
Gastritis/gastritis aggravated*	6.2	5.3
Flatulence	5.0	1.8
Diarrhea	6.7	3.0
Abdominal pain	3.7	2.4
Nausea/nausea aggravated	4.8	2.4
Vomiting/vomiting aggravated	3.3	1.2
Respiratory		
Respiratory infection	8.5	3.0

Adverse Reaction	Esomeprazole DR tablets (10, 20 & 40 mg) n = 519 (%)	Placebo n = 169 (%)
Sinusitis	4.2	1.8
Resistance Mechanism		
Viral infection	3.7	1.8
Miscellaneous		
Accident and/or injury	3.7	1.8

*endoscopic assessment

Additionally, the following adverse reactions (irrespective of causality) were each reported at a rate of >1% with esomeprazole magnesium in these same long-term studies (n=519): rash, fracture, hernia, dizziness, duodenitis, dyspepsia, epigastric pain, serum gastrin increased, gastroenteritis, GI mucosal discoloration, esophageal disorder, tooth disorder, SGPT (serum glutamic pyruvic transaminase) increased, hypertension, coughing, rhinitis, anemia, benign GI neoplasm, back pain, chest pain, and fatigue.

Clinical experience for up to one year in over 800 patients with doses of esomeprazole delayed release tablets of 40 mg have shown a similar adverse reaction pattern to that seen in short-term trials. In addition to the adverse reactions listed above, the following adverse reactions were reported (at a rate of more than 1%), irrespective of causal relationship (mean duration of treatment = 294 days): accident/injury (7.6%), pain (4.3%), urinary tract infection (3.7%), bronchitis (3.6%), arthralgia (2.9%), hypertension (2.6%), allergy (2.1%), insomnia (2.1%), hypercholesterolemia (2.0%), anxiety (1.7%), gastroesophageal reflux (1.6%), fever (1.5%), ear infection (1.5%), flu-like disorder (1.4%), myalgia (1.2%), arthropathy (1.1%), dyspnea (1.1%), overdose (1.1%).

H. pylori Eradication Combination Therapy

In clinical studies, a total of 446 patients received esomeprazole delayed release tablets in combination with amoxicillin and clarithromycin for 7 days. The following adverse reactions were reported (at a rate of more than 1%), irrespective of causal relationship: diarrhea (21.5%), taste perversion (12.6%), headache (3.6%), dry mouth (3.4%), SGPT increased (1.8%), flatulence (1.6%), nausea (1.3%), stomatitis (1.3%), vomiting (1.1%) and pharyngitis (1.1%). However, it should be noted that taste perversion is commonly associated with clarithromycin treatment and diarrhea is commonly associated with antibiotic treatment.

When MYLAN-ESOMEPRAZOLE is used in combination with amoxicillin and clarithromycin, the Product Monographs for those agents must be consulted and followed.

Healing of Gastric Ulcers Associated with NSAID Therapy

The data presented in this section is derived from two short-term gastric ulcer healing studies comprising 836 patients.

Table 3 Percentage of Patients reporting Adverse Reactions that were Assessed by the Investigator to have a reasonable causal relationship with Treatment (at a Rate of >1%) in Short Term Clinical Trials (up to 8 Weeks), for the healing of gastric ulcers associated with NSAID therapy.

Adverse Reactions	Esomeprazole DR tablets (20 & 40 mg qd) n = 556 (%)	Ranitidine (150 mg bid) n = 280 (%)
Gastrointestinal		
Flatulence	2.5	3.6
Gastritis	1.8	0.7
Diarrhea	1.6	0.7
Dyspepsia/Dyspepsia aggravated	1.6	2.5

The following adverse reactions occurred (<1% for esomeprazole delayed release tablets) in clinical trials for the healing of gastric ulcers associated with NSAID therapy, and were considered causally related by the investigator:

Gastrointestinal: abdominal pain, epigastric pain, gastric retention, gastric ulcer, gastroesophageal reflux, nausea, peptic ulcer aggravated
Liver and Bilary: abnormal hepatic function, increased SGOT, increased SGPT
Metabolic & Nutritional: increased phosphatase alkaline
Nervous System: headache
Psychiatric: insomnia
Special Senses: taste perversion

The following adverse events (considered unrelated to esomeprazole by the investigator) were each reported at a frequency of >1% in clinical trials for the healing of gastric ulcers; gastric ulcer aggravated, mucosal discoloration GI, gastrointestinal symptoms NOS, esophageal stricture, esophagitis, vomiting, constipation, duodenitis, rash, anxiety, pharyngitis, respiratory infection, sinusitis, urinary tract infection, accident and/or injury, and back pain.

In addition, the following adverse events of a potentially severe nature (considered unrelated to esomeprazole by the investigator) were reported in these same studies; cardiac failure aggravated, hypertension/hypertension aggravated, syncope, arrhythmia, bradycardia, atrial fibrillation, palpitation/palpitation aggravated.

Risk-reduction of Gastric Ulcers Associated with NSAID Therapy

The data presented in this section is derived from two long-term ulcer risk-reduction studies comprising 1390 patients.

Table 4 Percentage of Patients reporting Adverse Reactions that were Assessed by the Investigator to have a reasonable causal relationship with Treatment (at a Rate of >1%) in Long Term Clinical Trials (up to 6 months), for the risk-reduction of gastric ulcers associated with NSAID therapy.

Adverse Reaction	Esomeprazole DR tablets (20 & 40 mg qd) n = 936 (%)	Placebo n = 454 (%)
Gastrointestinal		
Flatulence	4.0	3.7
Gastritis/Gastritis aggravated	2.2	2.9
Gastrointestinal symptoms	2.0	2.6
Gastroesophageal reflux	1.9	3.5
Dyspepsia/Dyspepsia aggravated	1.9	3.7
Nausea/Nausea aggravated	1.7	2.0
Abdominal Pain	1.4	0.9
Diarrhea	1.1	0.9

The following adverse reactions occurred (<1% for esomeprazole magnesium) in clinical trials for the risk- reduction of gastric ulcers associated with NSAID therapy, and were considered causally related by the investigator:

Body as a Whole: asthenia, back pain
Blood System: anemia, leukopenia, thrombocytopenia
Gastrointestinal: constipation, defecation urge, duodenitis, epigastric pain, eructation, gastric retention, gastric ulcer, dry mouth, mucosal discolouration GI, frequent stools, vomiting
Liver and Bilary: hepatic enzymes increased NOS, increased SGOT, increased SGPT
Metabolic & Nutritional: dehydration, weight decrease, weight increase
Neoplasms: GI neoplasm
Nervous System: dizziness, headache, hyperesthesia, vertigo
Psychiatric: anorexia, increased appetite, insomnia, sleep disorder
Resistance Mechanism: herpes simplex
Skin: rash
Special Senses: taste perversion

The following adverse events (considered unrelated to esomeprazole by the investigator) were each reported at a frequency of >1% in clinical trials for the risk-reduction of gastric ulcers;

arthralgia, arthrosis, aggravated rheumatoid arthritis, cramps, myalgia, rash, urticaria, dizziness, headache, neuropathy, insomnia, constipation, duodenitis, epigastric pain, gastric mucosal lesion NOS, mucosal discoloration GI, esophageal disorder, esophagitis, vomiting, dry mouth, increased SGOT, increased SGPT, bronchitis, coughing, dyspnoea, pharyngitis, respiratory infection, sinusitis, anemia, thrombocythemia, micturation frequency, urinary tract infection, benign GI neoplasm, accident/or injury, back pain, chest pain, fatigue, peripheral edema, pain, and postoperative complications.

In addition, the following adverse events of a potentially severe nature (considered unrelated to esomeprazole by the investigator) were reported in these same studies; cardiac failure, hypertension/hypertension aggravated, tachycardia, palpitation, atrial fibrillation, extrasystoles, bradycardia, arrhythmia, myocardial fibrosis, coronary artery disorder, syncope, thrombocytopenia, leucopenia, and cholelithiasis.

Zollinger-Ellison Syndrome

In an open label, 12 month clinical study conducted in 21 patients with either Zollinger-Ellison syndrome or idiopathic hypersecretion, single cases of the following adverse events, not previously listed under other indications, were reported with esomeprazole delayed release tablets use, irrespective of causality: abdominal rigidity, asthma, Barrett's esophagus, carcinoid tumour of the stomach, carpal tunnel syndrome, depression, erosive gastritis, gingival abscess, hematuria, hyperparathyroidism, hypoesthesia, hypokalemia, hypomagnesemia, hypothyroidism, mean cell volume decreased, melena, muscle spasms, neoplasm progression, osteoporosis, parathesia, pharyngolaryngeal pain, postoperative pain, proteinuria, pruritus, rhinorrhea.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Skin: dermatitis, pruritus and urticaria
Nervous System: paresthesia

Rare Clinical Trial Adverse Drug Reactions (<0.1%)

Body as a Whole: malaise
Metabolic & Nutritional: hyponatremia

Very Rare Clinical Trial Adverse Drug Reactions (<0.01%)

Body as a Whole: muscular weakness
Hepatic & Biliary: hepatic encephalopathy

Abnormal Hematologic and Clinical Chemistry Findings

See ADVERSE REACTIONS – Post-Market Adverse Drug Reactions, and WARNINGS and PRECAUTIONS – Carcinogenesis and Mutagenesis.

Pediatrics (1-17 years of age)

In children (1 – 11 years) with Gastroesophageal Reflux Disease (GERD)

Adverse reactions have been recorded during a clinical investigation in 109 pediatric patients (1-11 years of age) exposed to esomeprazole delayed release tablets. There was an increase number of adverse events reported (irrespective of causality) in the > 20 kg treatment groups (mean age of 8.4 years old) versus the < 20 kg treatment group (mean age 2.3 years old), however there was no difference in the character of the adverse events reported by age group or dosing group. The most common reactions (irrespective of causality) which occurred with a frequency of >1% in clinical studies included vomiting, pyrexia, diarrhea and cough. The most frequently reported (at least 1%) treatment-related adverse events were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). No new safety concerns were identified.

In this study there were some inconsistent and minor changes (i.e. < 5 mmHg) in blood pressure (BP) which were not considered to be a drug effect. For most dosing groups there was a slight increase in mean systolic and diastolic BP values (< 5 mmHg) while for the 20 mg dosing group there was a slight decrease in mean systolic BP (< 1 mmHg). Overall, the mean BP values remained within normal limits. The interpretation of these inconsistent and minor changes is uncertain due to the lack of a placebo arm in this study.

No clinically important changes or trends were noted over time in clinical chemistry that were different from those already listed from adult studies (see Adults, Abnormal Hematologic and Clinical Chemistry Findings).

In children (12 – 17 years) with Gastroesophageal Reflux Disease (GERD)

In a multicentre, randomized, double-blind, parallel-group safety and tolerability study in 149 pediatric patients (12 – 17 years of age; 89 female, 124 Caucasian, 15 Black, 10 Other) with clinically diagnosed GERD), adverse events were recorded after exposure to esomeprazole magnesium 20 mg and 40 mg once daily for up to 8 weeks. Patients were not endoscopically characterized as to the presence or absence of erosive esophagitis.

The observed adverse event profile was found to be consistent with that seen in adults, with treatment related events of headache (8.1%), abdominal pain (2.7%), diarrhea (2.0%), and nausea (2.0%) commonly reported. No new safety concerns were identified for this population.

Post-Market Adverse Drug Reactions

From post-marketing experience there have been uncommon reports (<1%) of peripheral edema, insomnia, paresthesia, somnolence, vertigo, increased liver enzymes.

There have been rare reports (<0.1%) of blurred vision, hypersensitivity reactions (e.g. angioedema, anaphylactic reaction/shock), myalgia, leukopenia, thrombocytopenia, depression, alopecia, hepatitis with or without jaundice, hyponatremia, agitation, confusion, taste

disturbance, bronchospasm, stomatitis, GI candidiasis, rash, dermatitis, photosensitivity, arthralgia, malaise, and hyperhidrosis.

Very rarely (<0.01%) agranulocytosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pancytopenia, aggression, hallucination, hepatic failure, hepatic encephalopathy, interstitial nephritis, muscular weakness, gynecomastia, hypomagnesaemia (severe hypomagnesaemia may result in hypocalcaemia, and hypomagnesaemia may also result in hypokalaemia) and microscopic colitis have been reported.

As of 25 July 2007, 28 medically confirmed case reports with 59 adverse events in children between 1 and 11 years of age. All cases constituted off-label use. An overall assessment of the adverse events reported in children ages 1-11 years raised no safety concerns with esomeprazole treatment in this age group.

As of 25 June 2007, 48 medically confirmed case reports with 84 adverse events in children between 12 and 17 years of age. Five of the 48 cases were reported within approved label use, while 43 cases constituted off-label use. An overall assessment of the adverse events reported after within-label and off-label use in children ages 12-17 years raised no safety concerns with esomeprazole treatment in this age group**.**

Gastrointestinal: Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.

Musculoskeletal and Connective Tissue: Osteoporosis and osteoporosis-related fractures have been reported with multiple daily doses and long-term PPI therapy.
There have been post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see WARNINGS AND PRECAUTIONS, Immune).

DRUG INTERACTIONS

Overview

Esomeprazole magnesium is metabolized by the cytochrome P-450 system (CYP), mainly in the liver, through CYP 2C19 and CYP 3A4. There are no clinically significant interactions between esomeprazole and diazepam, phenytoin, quinidine or cisapride*. Drugs known to inhibit CYP 2C19 or CYP 3A4 or both (such as clarythromycin and voriconazole) may lead to increased esomeprazole serum levels by decreasing the rate of esomeprazole's metabolism.
Drugs known to induce CYP 2C19 or CYP 3A4 or both (such as rifampin and St. John's Wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

*not marketed in Canada

With on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole, should be considered when esomeprazole delayed release tablets are prescribed in this manner (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

Diazepam: Concomitant administration of esomeprazole delayed release tablets (30 mg once daily for 5 days) resulted in a 45% decrease in the clearance of diazepam in healthy male volunteers. Studies in females have not been conducted. Increased levels of diazepam were seen some 12 hours after dosing and later when the plasma levels of diazepam were below its therapeutic range. Therefore, this interaction is unlikely to be of clinical significance.

Warfarin: Concomitant administration of 40 mg esomeprazole delayed release tablets (once daily for 3 weeks) to male and female patients on stable anticoagulation therapy with warfarin, resulted in a 13% increase in trough plasma levels of R-warfarin (the less potent enantiomer) while that of S-warfarin was unchanged. Coagulation times were stable throughout the entire study period. No clinically significant interaction was observed. However, from post marketed use, cases of elevated international normalized ratio (INR) of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives (please refer to approved Product Monograph for warfarin or relevant coumarin derivative).

Cilostazol*: Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites, 3,4-dihydrocilostazol, by 29% and 69% respectively.

*not marketed in Canada

Clopidogrel: Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75mg daily maintenance dose) and esomeprazole (40 mg once daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

It is, however, uncertain to what extent this interaction is clinically important. One prospective, randomized (but incomplete) study (in over 3 760 patients comparing placebo with omeprazole 20 mg in patients treated with clopidogrel and ASA) and non-randomized, post-hoc analyses of data from large, prospective, randomized clinical outcome studies (in over 47 000 patients) did not show any evidence of an increased risk for adverse cardiovascular outcome when clopidogrel and PPIs, including esomeprazole, were given concomitantly.

Results from a number of observational studies are inconsistent with regard to increased risk or no increased risk for CV thromboembolic events when clopidogrel is given together with a PPI.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the

clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA (see WARNINGS and PRECAUTIONS, General).

Tacrolimus: Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Phenytoin: Concomitant administration of 40 mg esomeprazole delayed release tablets (once daily for 2 weeks) to male and female epileptic patients stabilized on phenytoin, resulted in a 13% increase in trough plasma levels of phenytoin. This minor interaction is unlikely to be of clinical relevance as dose reduction was not required in any patient nor was the profile and frequency of adverse events affected.

Results from a range of interaction studies with esomeprazole magnesium versus other drugs indicate that daily doses of 40 mg esomeprazole delayed release tablets, given for 5 to 21 days in male and/or female subjects, has no clinically relevant interactions with CYP 1A2 (caffeine), CYP 2C9 (S-warfarin), and CYP 3A (quinidine, estradiol and cisapride*).

*not marketed in Canada

Methotrexate: Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) 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; General).

Voriconazole: Concomitant administration of esomeprazole with a combined inhibitor of CYP 2C19 and CYP 3A4 may result in more than double the levels of esomeprazole exposure.

As with all drugs that reduce gastric acidity, changes in plasma levels of other drugs whose absorption is pH dependent (e.g. ketoconazole, itraconazole or erlotinib) must be taken into account when co-administered with esomeprazole. The absorption of ketoconazole, itraconazole or erlotinib can decrease during treatment with esomeprazole.

Digoxin: The absorption of digoxin can increase during treatment with esomeprazole and other drugs that reduce gastric acidity. Concomitant treatment with omeprazole (20 mg daily) and digoxin in ten healthy subjects increased the bioavailability of digoxin by an average of 10% (up to 30% in two out of ten subjects).

Antiretroviral Drugs:

Rilpivirine: Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS).

Atazanavir: Co-administration of MYLAN-ESOMEPRAZOLE with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily)

substantially reduced plasma Cmax and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir (see REYATAZ Product Monograph).

Nelfinavir: Co-administration of MYLAN-ESOMEPRAZOLE with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg once daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and Cmax for nelfinavir (by 36% and 37%, respectively and its active metabolite M8 (by 92% and 89%, respectively) (see VIRACEPT Product Monograph).

Saquinavir: Co-administration of saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir, due to increased saquinavir exposure and thus the risk of saquinavir-related toxicities (see the INVIRASE Product Monograph).

Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased squinavir AUC by 82% and Cmax by 75%.

Drug-Food Interactions

Food intake delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Drug-Laboratory Interactions

During treatment with antisecretory drugs, CgA increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, MYLAN-ESOMEPRAZOLE treatment should be stopped 14 days before CgA measurement (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The tablets should be swallowed whole with sufficient water.

- The tablets may also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

- Dispersed tablets can also be administered via naso-gastric feeding tubes (8-20 French) using a 25 to 60 mL disposable syringe. The type of syringe used should ensure a secure fit with the feeding tube. Each esomeprazole delayed release tablet should be dispersed in 50 mL of water and passed through the tube into the stomach. After administering the suspension, the naso-gastric tube may be flushed with an additional 25-50 mL of water

to clear the syringe and tube. In larger naso-gastric feeding tubes (i.e. 14 French or larger), the dispersion volume may be reduced to 25 mL.

Recommended Dose and Dosage Adjustment

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

Adults

Treatment of conditions where a reduction of gastric acid secretion is required:

Reflux Esophagitis: The recommended dose in patients with reflux esophagitis is 40 mg MYLAN-ESOMEPRAZOLE once daily for 4 to 8 weeks in order to optimize the healing rate and symptom resolution. Healing occurs in the majority of patients within 4 weeks. Sustained freedom from symptoms is achieved rapidly for most patients. An additional 4 weeks of treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.

Maintenance of Healing of Erosive Esophagitis: For the long-term treatment of patients whose reflux esophagitis has been healed with acid suppression therapy, the recommended dose is 20 mg MYLAN-ESOMEPRAZOLE once daily. Controlled studies do not extend beyond 6 months.

Nonerosive reflux disease: In patients with heartburn and/or acid regurgitation, without esophagitis, the recommended dose is 20 mg MYLAN-ESOMEPRAZOLE once daily for 2 to 4 weeks. If symptom control is not achieved after 4 weeks of treatment, further investigation is recommended.

Maintenance Treatment of NERD (On-demand): For the maintenance of symptom relief in patients whose symptoms were initially controlled after daily doses for 2 to 4 weeks, the recommended dose is 20 mg MYLAN-ESOMEPRAZOLE once daily taken as needed. Despite treatment, the possibility for development of esophagitis in patients cannot be excluded.

Healing of Gastric Ulcers Associated with NSAID Therapy: In patients requiring NSAID therapy, the recommended dose is 20 mg MYLAN-ESOMEPRAZOLE once daily for 4 to 8 weeks. No additional clinical benefit was observed for the 40 mg dose over the 20 mg dose.

Risk-Reduction of Gastric Ulcers Associated with NSAID Therapy: In patients requiring NSAID therapy who are at risk of gastric ulcers, the recommended dose is 20 mg MYLAN-ESOMEPRAZOLE once daily. No additional clinical benefit was observed for the 40 mg dose over the 20 mg dose. Controlled studies did not extend beyond 6 months.

Zollinger-Ellison Syndrome: The dosage in patients with pathological hypersecretory conditions varies with each individual. The recommended initial dosage is 40 mg MYLAN-ESOMEPRAZOLE twice a day. Dosages should then be adjusted to individual patient's needs and treatment should continue as long as clinically indicated. A small number of

patients have been treated with doses up to 80 mg t.i.d. In a clinical study, 90% of patients (19 out of 21) with a hypersecretory condition such as Zollinger-Ellison syndrome had gastric acid outputs appropriately controlled at various doses and were maintained through 12 months (see Clinical Trials; In Patients with Zollinger-Ellison Syndrome). Safety information is limited in doses above 80 mg a day.

Helicobacter pylori Eradication:

In patients with H. pylori-associated active duodenal ulcer: The recommended dose is MYLAN-ESOMEPRAZOLE 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days. No further treatment with MYLAN-ESOMEPRAZOLE is required to ensure healing and/or symptom control.

In patients with a history of duodenal ulcer: The recommended dose is MYLAN-ESOMEPRAZOLE 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Pediatrics (1-17 years of age)

Treatment of conditions where a reduction of gastric acid secretion is required:

Children (1-11 years of age)

Reflux Esophagitis: The recommended dose in patients with reflux esophagitis is:

Weight < 20 kg:	10 mg MYLAN-ESOMEPRAZOLE once daily for 8 weeks
Weight ≥ 20 kg:	10 mg or 20 mg MYLAN-ESOMEPRAZOLE once daily for 8 weeks

Safety studies do not extend beyond 8 weeks.

Nonerosive Reflux Disease (NERD): In children with heartburn and/or acid regurgitation, without esophagitis, the recommended dose is 10 mg MYLAN-ESOMEPRAZOLE once daily for up to 8 weeks. Safety studies do not extend beyond 8 weeks.

Doses over 1 mg/kg/day have not been studied. There are currently no data on appropriate doses for children with hepatic impairment (see also WARNINGS AND PRECAUTIONS).

Children (12-17 years of age)

No dose adjustment is required (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Pediatrics).

Reflux esophagitis: The recommended dose in patients with reflux esophagitis is 20 mg or 40 mg MYLAN-ESOMEPRAZOLE once daily for 4 to 8 weeks. Safety studies do not extend beyond 8 weeks.

Nonerosive Reflux Disease (NERD): In patients with heartburn and/or acid regurgitation, without esophagitis, the recommended dose is 20 mg MYLAN-ESOMEPRAZOLE once daily for 2 to 4 weeks. If symptom control is not achieved after 4 weeks of treatment, further investigation is recommended. Safety studies do not extend beyond 8 weeks.

Missed Dose

A missed dose should be taken as soon as possible within 12 hours. If more than 12 hours have passed, then the next scheduled dose should be taken at the appropriate time.

Administration

Special Populations

When used in combination with amoxicillin and clarithromycin, please refer to the Product Monographs of these drugs for prescribing information regarding Contraindications, Warnings and Dosing (in elderly and patients with renal and hepatic insufficiency).

Patients with Renal Insufficiency: No dose adjustment is required (see WARNINGS AND PRECAUTIONS).

Patients with Hepatic Insufficiency: No dose adjustment is required for patients with mild to moderate hepatic impairment. The daily doses of 20 mg in patients with severe hepatic impairment should not, as a rule, be exceeded (see WARNINGS AND PRECAUTIONS).

Elderly Patients: No dose adjustment is required (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Limited information is available on the effects of higher doses in man, and specific recommendations for treatment cannot be given. Experience from a patient who deliberately ingested an overdose of esomeprazole (280 mg), demonstrated symptoms that were transient, and included weakness, loose stools and nausea. Single doses of 80 mg MYLAN-ESOMEPRAZOLE (esomeprazole) have been shown to be uneventful. No specific antidote is known. Esomeprazole is extensively protein-bound and is therefore not readily dialyzable. Treatment should be symptomatic and general supportive measures should be utilized.

The maximum non-lethal oral dose in male and female rats ranged from 240 to 480 mg/kg (see TOXICOLOGY).

When used in combination with antibiotics, the Prescribing Information/Product Monograph for those antibiotics should be consulted.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MYLAN-ESOMEPRAZOLE (esomeprazole delayed release tablets) contain esomeprazole (the S-isomer of omeprazole). Esomeprazole is acid labile and therefore is administered orally as enteric-coated granules compressed into a tablet.

Esomeprazole magnesium (a substituted benzimidazole), reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the gastric enzyme H^+,K^+-ATPase (the proton pump) which is responsible for acid secretion by the parietal cells of the stomach.

Pharmacodynamics

Esomeprazole accumulates in the acidic environment of the parietal cells after absorption, where it is converted into the active form. This active sulphenamide specifically binds the H^+, K^+-ATPase (proton pump), to block the final step in acid production, thus reducing gastric acidity. Esomeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion.

In healthy male subjects (n=12), repeated administration with 20 mg esomeprazole magnesium once daily for 5 days, decreased mean peak acid output after pentagastrin stimulation by 90% when measured 6 to 7 hours after dosing.

The effect of antisecretory therapy can be predicted from the duration of suppression of intragastric acidity to above pH 4.0 achieved by each drug regimen, and the length of treatment.

The antisecretory activity of esomeprazole magnesium was studied in patients with nonerosive reflux disease. Esomeprazole tablets 20 and 40 mg tablets were administered over 5 days and the proportion of time when intragastric pH was >4 over a 24 hour period was assessed on Day 5, as shown in the following table:

Table 5 Effect on Intragastric pH on Day 5 (n=36)

Parameter	Esomeprazole DR tablets 40 mg	Esomeprazole DR tablets 20 mg
% time gastric pH >4* (hours)	70% ** (16.8 hours)	53% (12.7 hours)
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 DR tablets 40 mg vs. Esomeprazole DR tablets 20 mg

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued 14 days prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range (see WARNINGS AND PRECAUTIONS, Interference with Laboratory Tests).

Eradication of *Helicobacter pylori*: Infection with *H. pylori* is associated with peptic ulcer disease and is a major factor in the development of gastritis. Approximately 90 to 100% of patients with duodenal ulcers, and 80% of patients with gastric ulcer, are infected with *H. pylori.* Treatment with esomeprazole delayed release tablets alone has been shown to suppress, but not eradicate *H. pylori.*

Eradication of *H. pylori* with triple therapy consisting of esomeprazole delayed release tablets and clarithromycin/amoxicillin for seven days is associated with healing and improvement of symptoms of duodenal ulcers.

Pharmacokinetics

Absorption of esomeprazole in healthy subjects results in peak plasma levels occurring 1 to 2 hours after dosing. The systemic bioavailability is 64% after a single 40 mg dose and 89% after repeated once daily oral administration (40 mg for 5 days). The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound and optically stable in vivo, with negligible inversion to the other isomer.

A pharmacokinetic profile of esomeprazole was studied in 36 patients with NERD after repeated once daily administration of 20 mg and 40 mg.

Table 6 Pharmacokinetic Parameters of Esomeprazole After Oral Administration for 5 days. Mean (% CV)

Parameters	Esomeprazole DR tablets 40 mg	Esomeprazole DR tablets 20 mg
$AUC_{(tot)}$ (μmol*h/L)	12.6 (42%)	4.2 (59%)
C_{max} (μmol/L)	4.7 (37%)	2.1 (45%)
T_{max} (h)	1.6 (50%)	1.6 (86%)
$t_{1/2}$ (h)	1.5 (32%)	1.2 (37%)

Values represent geometric mean except the $T_{max,}$ which is the arithmetic mean.

Food intake delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Pharmacokinetics in combination with antibiotics: Interactions between esomeprazole (20 mg b.i.d.), amoxicillin (1 g b.i.d.) and clarithromycin (500 mg b.i.d.), were evaluated in a 4-way cross-over study (each study period was 7 days). When given as the triple combination, the bioavailability (AUC and C_{max}) of amoxicillin and clarithromycin were not significantly changed in healthy volunteers, compared with either drug given alone. The AUC and C_{max} of the 14-hydroxyclarithromycin metabolite were both increased by 53% during dosing with the triple combination, compared to values following dosing with clarithromycin alone. There were also significant increases in the AUC (two-fold increase) and C_{max} (39%) values for esomeprazole during concomitant administration with the antibiotic drugs, compared with esomeprazole alone.

Metabolism

Esomeprazole is completely metabolized by the cytochrome P-450 system, mainly in the liver (via CYP 2C19 and CYP 3A4). The major metabolites of esomeprazole (hydroxy and desmethyl metabolites) have no effect on gastric acid secretion. The CYP 2C19 isozyme, which is involved in the metabolism of all available proton pump inhibitors, exhibits polymorphism. Some 3% of Caucasians and 15-20% of Asians lack CYP 2C19 and are termed "poor metabolizers". At steady state (40 mg for 5 days), the ratio of AUC in poor metabolizers to AUC in the rest of the population is approximately 2. Dosage adjustment of esomeprazole delayed release tablets based on CYP 2C19 status is not necessary.

Almost 80% of an oral dose of esomeprazole is excreted as metabolites in urine with the remainder recovered in feces. Less than 1% of the parent drug is found in urine. Total recovery from urine and feces is 92 to 96% within 48 hours of a single oral dose.

Special Populations and Conditions

Pediatrics (1 – 17 years of age)

Children (1 – 11 years of age): The pharmacokinetics of esomeprazole were studied in 31 pediatric patients with GERD 1 to 11 years of age inclusive, in a single centre study. Patients were divided into 2 subgroups by age. For ages 1 to 5, patients received esomeprazole 5 mg or

10 mg once daily for 5 days. For ages 6 to 11 years, patients received esomeprazole 10 mg or 20 mg once daily for 5 days.

Following repeated dose administration of esomeprazole 10 mg and 20 mg, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) for the 10 mg dose was similar across the 1 – 11 year-olds and similar to the total exposure seen with the 20 mg dose in adults. The 20 mg dose resulted in higher exposure in 6 – 11 year-olds compared to adults.

Repeated dose administration of 5 mg esomeprazole resulted in insufficient exposure in 1 – 5 year-olds.

Table 7 Summary of Pharmacokinetic Parameters in 1-11 year olds with GERD following of 5-days of once-daily oral esomeprazole treatment.

	1 to 5 year-olds		6 to 11 year-olds	
	5 mg (n= 6)	**10 mg (n= 8)**	**10 mg (n= 7)**	**20 mg (n= 6)**
$AUC_{(tot)}$ (µmol*h/L)	0.74	4.83	3.70	6.28
C_{max} (µmol/L)	0.62	2.98	1.77	3.73
T_{max} (h)	1.33	1.44	1.79	1.75
$t_{1/2}$ (h)	0.42	0.74	0.88	0.73
Cl/F (L/h)	19.44	5.99	7.84	9.22

Values represent geometric mean except the $T_{max,}$ which is the arithmetic mean.

(see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Children (12-17 years of age): The pharmacokinetics of esomeprazole were studied in 28 pediatric patients with GERD aged 12 to 17 years, in a single centre randomized study. Patients received esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age. More than dose-proportional increases in mean C_{max} and AUC values were observed between the two groups in the study. Overall, esomeprazole pharmacokinetics in pediatric patients aged 12 to 17 years were similar to those observed in adult patients with NERD.

Table 8 Comparison of pharmacokinetic parameters in 12 -17 year olds with GERD and adults with NERD following esomeprazole daily repeated oral dosing*

Pharmacokinetic Parameter	**Pediatrics (aged 12-17 years) (n = 28)**		**Adults (≥18 years) (n= 36)**	
	20 mg	**40 mg**	**20 mg**	**40 mg**
AUC (µmol*h/L)	3.65	13.86	4.2	12.6
C_{max} (µmol/L)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
$t_{1/2\,\lambda z}$ (h)	0.82	1.22	1.2	1.5

Data presented are geometric means for AUC, C_{max} and $t_{1/2\,\lambda z}$ and median value for t_{max}

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

Geriatrics: The metabolism of esomeprazole delayed release tablets is not significantly changed in elderly subjects. Following repeated oral dosing with 40 mg esomeprazole delayed release tablets in healthy elderly subjects (6 males, 8 females; 71 to 80 years of age), AUC and C_{max} values measured were similar to those previously measured in young GERD patients (ratio of AUC values in elderly vs. GERD subjects: 1.25; ratio of C_{max} values: 1.18).

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: (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Renal Insufficiency: (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Poor Metabolizers: (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

STORAGE AND STABILITY

Temperature: Store in a dry place at controlled room temperature (15-30°C).

Moisture: MYLAN-ESOMEPRAZOLE (esomeprazole) delayed release tablets are moisture-sensitive.

Others: Keep in a safe place out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

Esomeprazole is acid labile and therefore is administered orally as a MUPS™ tablet. The MUPS™ tablet consists of many enteric-coated granules compressed into a tablet.

MYLAN-ESOMEPRAZOLE 20 mg tablets are light pink, oblong and biconvex, engraved with “20 mg” on one side and “A” over “EH” on the other side.

MYLAN-ESOMEPRAZOLE 40 mg tablets are pink, oblong and biconvex, engraved with “40 mg” on one side and “A” over “EI” on the other side.

The 20 mg tablets are available in high-density polyethylene (HDPE) bottles of 100 tablets. The 40 mg strength is available in high-density polyethylene (HDPE) bottles of 100 tablets. Desiccant is included in the bottle.

Information for the patient is provided as a package insert in the MYLAN-ESOMEPRAZOLE cartons.

Composition

MYLAN-ESOMEPRAZOLE 20 mg and 40 mg tablets contain the following non-medicinal ingredients: cellulose microcrystalline, crospovidone, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, iron oxide, magnesium stearate, methacrylic acid ethylacrylate copolymer, polyethylene glycol, polysorbate, synthetic paraffin, sodium stearyl fumarate, sugar spheres, talc, titanium dioxide and triethyl citrate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

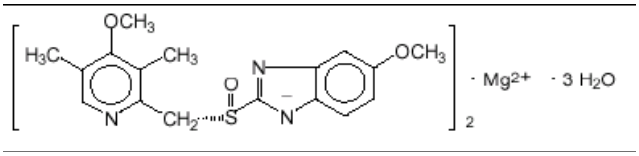
Common Name: esomeprazole magnesium trihydrate

Chemical Name: Di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]- 1H-benzimidazole magnesium trihydrate

Molecular Formula: $C_{34}H_{36}N_6O_6S_2Mg \bullet 3H_2O$

Molecular Mass: 767.2 g/mol (trihydrate)
713.3 g/mol (anhydrous basis)

Structural Formula:



Physicochemical Properties: Esomeprazole magnesium is a white to slightly coloured crystalline powder, containing 3 water molecules of hydration. The solubility in water is 0.3 mg/mL, and the solubility in methanol is initially high, but followed by precipitation of a crystalline dihydrate. The pKa of the benzimidazole (omeprazole base) is 8.8, and that of the pyridinium ion, 4.0.

CLINICAL TRIALS

Study demographics and trial design

Reflux Esophagitis

Initial Therapy: A meta-analysis of data from 4 randomized, double-blind clinical trials demonstrated the efficacy of esomeprazole magnesium 40 mg in the acute treatment of reflux esophagitis. Healing was observed in over 93% (PP analysis) of patients following 8 weeks of treatment and was associated with symptom relief.

Maintenance of healing of Erosive Esophagitis: For maintenance treatment of reflux esophagitis, esomeprazole magnesium 20 mg once daily maintained healing of reflux esophagitis and provided symptom relief in the majority of patients (79-93%) over a 6 month period.

Nonerosive Reflux Disease

In five large, multicentre, randomized, double-blind clinical trials, treatment with esomeprazole magnesium 20 or 40 mg daily for 4 weeks was compared to treatment with omeprazole 20 mg daily or placebo, regarding the complete resolution of heartburn in patients with nonerosive reflux disease (i.e. without macroscopic esophagitis). All active treatments were highly successful, safe and well-tolerated. Treatment with esomeprazole magnesium (20 or 40 mg) provided patients with significantly more heartburn-free days and nights than placebo.

Maintenance Treatment of NERD (On-demand)

Patients with complete resolution of heartburn following initial treatment for NERD were randomized to double-blind treatment with esomeprazole delayed release tablets 40 mg, 20 mg or placebo, once daily when needed to control symptoms of GERD for 6 months. Time to discontinuation due to unwillingness to continue with current therapy was the primary efficacy variable. Esomeprazole delayed release tablets (20 and 40 mg) was better than placebo with significantly fewer patients discontinuing treatment and by maintaining sufficient control of heartburn in significantly more patients than placebo treatment.

Table 9 Results of on-demand treatment studies of patients with symptoms of GERD, without macroscopic esophagitis. Proportion of patients unwilling to continue on-demand therapy, ITT analysis.

	Esomeprazole DR tablets 40 mg	Esomeprazole DR tablets 20 mg	Placebo
Study 1 (n=721)	11%	8%	42%
Study 2 (n=376)	10%	-	33%
Study 3 (n=342)	-	14%	51%

NSAID Associated Upper GI Ulcers

In clinical trials, treatment with esomeprazole delayed release tablets (20 mg or 40 mg) once daily was effective, safe and well-tolerated in combination with continuous NSAID use.

Healing of Gastric Ulcers in Patients Requiring NSAID Therapy, Including COX-2 Selective NSAIDs: Two multicentre, randomized, double-blind, active-controlled clinical trials were undertaken in 809 patients (ITT analysis) for up to 8 weeks to compare the effects of esomeprazole delayed release tablets (40 mg or 20 mg qd) against ranitidine (150 mg bid) in the healing of gastric ulcers in patients using non-selective or COX-2-selective NSAIDs. Patients enrolled in these studies had a gastric ulcer greater than or equal to 5 mm in diameter, ranged in age from 18 to 88 (mean age of 58 years) with 32% males and 68% females having a race distribution of 82% Caucasian, 5% Black, 7% Oriental and 12% other. Among these patients 85% were taking non-selective NSAIDs and 15% were on COX-2 selective NSAIDs. *H. pylori* status of patients at screening was 77% negative and 23% positive.

The results of these two studies are presented below:

Table 10 Observed Gastric Ulcer Healing rates in complete ITT population regardless of NSAID type.

	Study 5			Study 6			Pooled		
	E40 n=129	**E20 n=138**	**R150 n=132**	**E40 n=133**	**E20 n=138**	**R150 n=139**	**E40 n=262**	**E20 n=276**	**R150 n=271**
Ulcer healing rate at 4 weeks (%)	78.3	79.0	66.7	70.7	72.5	55.4	74.4	75.7	60.9
p-value[a]	0.036[b]	0.023[b]	-	0.009[b]	0.003[b]	-	<0.001[b]	<0.001[b]	-
Ulcer Healing rate at 8 weeks (%)	91.5	88.4	74.2	85.7	84.8	76.3	88.6	86.6	75.3
p-value[a]	<0.001[b]	0.003[b]	-	0.047	0.073	-	<0.001[b]	<0.001[b]	-

E20 = esomeprazole 20 qd; E40 = esomeprazole 40 mg qd; R150 = ranitidine 150 mg bid.

a chi-square p-value vs. Ranitidine 150 mg bid

b statistically significant vs. R150 (Hochberg adjusted)

Table 11 Observed GU healing status divided by NSAID usage at Week 4 and Week 8: (ITT pooled population).

NSAID Type Healed GU status	E40 N=262 n/N (%)	E20 N=276 n/N (%)	R150 N=271 n/N (%)
WEEK 4			
Nonselective NSAIDS			
Observed GU healing rate	164/225 (72.9)	179/242 (74.0)	129/219 (58.9)
Chi-square p-value[a]	0.002[b]	0.001[b]	
COX-2 selective			
Observed GU healing rate	31/37 (83.8)	30/34 (88.2)	35/50 (70.0)
Chi-square p-value[a]	0.137	0.050[b]	
WEEK 8			
Nonselective NSAID			
Observed GU healing rate	197/225 (87.6)	208/242 (86.0)	163/219 (74.4)
Chi-square p-value[a]	<0.001[b]	0.002[b]	
COX-2 selective			
Observed GU healing rate	35/37 (94.6)	31/34 (91.2)	40/50 (80.0)
Chi-square p-value[a]	0.051	0.165	

E20 = esomeprazole 20 qd; E40 = esomeprazole 40 mg qd; R150 = ranitidine 150 mg bid.

a p-value versus R150.

b statistically significant.

Note: Two patients in the R150 group (1 from each study) were not taking any NSAID medication before or during the study and were classified as "No Value," and were not included in this table. COX-2 selective NSAID is defined as patients who were on COX-2 monotherapy for 4 weeks prior to baseline EGD;
Nonselective NSAID is defined as patients who were on any other NSAID medication or a combination therapy of COX-2 selective plus non-selective NSAID medication during the 4 weeks prior to baseline EGD.

Risk-Reduction of Gastric Ulcers Associated with NSAID Therapy, Including COX-2 Selective NSAIDs: In two large multicentre, randomized, double-blind placebo-controlled trials, esomeprazole delayed release tablets (40 mg or 20 mg qd) was compared to placebo for the risk reduction of gastric ulcers associated with NSAID therapy in 1378 patients (ITT analysis). Patients enrolled in these studies ranged in age from 21 to 89 (mean age of 65 years) with 29% males and 71% females having a race distribution of 82% Caucasian, 5% Black, 4% Oriental and 8% other. Among these patients 71% were taking non-selective NSAIDs and 29% were on COX-2 selective NSAIDs. *H. pylori* status of patients at screening was 88% negative, 11% positive and 1% unknown. Patients at risk of an ulcer using either non-selective or COX-2-selective NSAIDs, were treated over a 6 month period. Patients treated with esomeprazole delayed release tablets 40 mg or 20 mg had significantly higher estimated ulcer-free rates compared to placebo as shown below.

In both risk-reduction studies an ulcer was defined qualitatively as having; a base (circular or elliptical white or grey-white punched-out defect in the mucosa that could be smooth and regular); a margin (discrete, sharply demarcated, regular, smooth, and usually raised in relation

to the ulcer base) and lack of an associated mass lesion or other features suggesting malignancy. Study 13 was considered the pivotal trial due to the fact that quantitative ulcer diameter measurements were recorded. It was demonstrated that esomeprazole 20 and 40 mg patients had a significant reduction in ulcer (≥ 5 mm) frequency compared to placebo (both p = 0.01). Study 14 was considered supportive as no ulcer diameter measurements accompanied the qualitative ulcer definition in this trial.

Table 12 Proportion of patients without gastric or duodenal ulcer by Month 6 in an ITT population.

	Study 13			Study 14		
	E40 (n=196)	**E20 (n=192)**	**Placebo (n=185)**	**E40 (n=271)**	**E20 (n=267)**	**Placebo (n=267)**
Response Rate (%)	95.9%	95.3%	89.2%	95.9%	95.5%	82.8%
p-value*	0.0074	0.0180	-	<0.0001	<0.0001	-

E20 = esomeprazole 20 qd; E40 = esomeprazole 40 mg qd
*Log rank test p-value (vs. Placebo)

In Patients with Zollinger-Ellison Syndrome

In an open label clinical trial in 21 patients with a hypersecretory condition such as Zollinger-Ellison syndrome or idiopathic hypersecretion (19 ZES, 2 IH), 90% of all patients (19 of 21) were treated successfully with esomeprazole delayed release tablets doses from 40 mg to 80 mg twice daily, with 1 patient receiving 80 mg t.i.d., for up to 12 months. For the trial duration, 14 of 21 patients were maintained and controlled on an esomeprazole delayed release tablets dose of 40 mg b.i.d., and 5 patients were maintained and controlled on esomeprazole delayed release tablets doses above 80 mg/day. Basal acid levels were maintained well below the targets of ≤ 10 mEq/h (or ≤ 5 mEq/h in patients who have undergone previous acid- reducing surgery) in 90% of all patients (19 of 21) on 80 – 240 mg esomeprazole delayed release tablets per day. Esomeprazole was generally well tolerated in this patient population (see ADVERSE REACTIONS; Zollinger-Ellison syndrome). Safety information does not extend beyond 1 year for esomeprazole delayed release tablets doses 80 mg daily or higher, and was from a limited study population.

In Patients with H. pylori-Associated Active Duodenal Ulcer

Ninety-five to 100% of duodenal ulcer and 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy.

Table 13 Results of a Study in Patients With Active Duodenal Ulcer Who Were H. Pylori-Positive.

Treatment	Eradication Rate		Ulcer Healing Rate
	ITT analysis	PP analysis	Post-Treatment (PP analysis)
esomeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	88.9%	86.0%	91.1% (94.1%)
omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week followed by omeprazole 20 mg daily for 3 weeks*	89.6%	87.7%	92.2% (95.6%)
omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week (no omeprazole follow-up)	87%*	78%*	92%*

Patients with duodenal ulcer, included in the ITT analysis, were assessed for H. pylori status by UBT, HUT® (test and histology pre- and post-treatment, n=433 (ITT analysis).
* Historical data from Losec® (omeprazole) Product Monograph.

In patients with a history of duodenal ulcer

Eradication of *H. pylori* is associated with long-term remission of peptic ulcer disease. Long-term treatment of these patients with anti-secretory agents is generally not recommended.

Table 14 Results of a Study in Patients With a History of Duodenal Ulcer Who Were H. Pylori-Positive.

Treatment	Eradication Rate	
	ITT Analysis	PP Analysis
esomeprazole magnesium trihydrate 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	89.7%	90.6%
omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	87.8%	91.4%

Patients included in the ITT and PP analyses were assessed for *H. pylori* status by UBT pre- and posttreatment, n=400 (ITT analysis).

In pediatrics (1-17 years of age)

Children (1-11 years of age) with Gastroesophageal Reflux Disease (GERD)

In a multicentre, parallel-group study, 109 pediatric patients with endoscopically-proven GERD (1-11 years of age; 53 female; 89 Caucasian, 19 Black, 1 Other) were treated with esomeprazole delayed release tablets 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. This study was not powered to demonstrate healing efficacy.

Of the 109 patients, 53 patients 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.

The use of esomeprazole delayed release tablets in pediatric patients (1 to 11 years of age) for the treatment of GERD is supported by extrapolation of results already included in the currently approved labelling from a) adequate and well-controlled studies in adults that supported the approval of esomeprazole delayed release tablets for adults, and additionally from b) safety and a pharmacokinetic study performed in pediatric patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Pediatrics and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pediatrics and CLINICAL TRIALS, Reflux Esophagitis and Nonerosive Reflux Disease).

Children (12-17 years of age) with Gastroesophageal Reflux Disease (GERD)

In a multicentre, randomised, double-blind, parallel study (n=149; 89 female, 124 Caucasian, 15 Black, 10 Other) pediatric patients (12-17 years of age) with clinically diagnosed GERD were treated with either esomeprazole delayed release tablets 20 or 40 mg once daily for up to 8 weeks to evaluate safety and tolerability. Patients were not endoscopically categorized as to the presence or absence of reflux esophagitis.

The use of esomeprazole delayed release tablets in pediatric patients (12 to 17 years of age) for the treatment of GERD is supported by extrapolation of results already included in the currently approved labelling from a) adequate and well-controlled studies in adults that supported the approval of esomeprazole magnesium for adults, and additionally from b) safety and pharmacokinetic studies performed in pediatric patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Pediatrics and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Pediatrics and CLINICAL TRIALS, Reflux Esophagitis and Nonerosive Reflux Disease).

Comparative Bioavailability Studies

In a single-centre, open-label, randomized, 3-way crossover comparative bioavailability study in which 96 healthy male and female volunteers received single doses of esomeprazole 40 mg, either as a pellets based sachet formulation, a capsule, or a commercial tablet, under fasting conditions, the 90% CIs for the ratio (sachet/capsule) of the geometric means for AUC_T and C_{max} were contained in the interval 80-125%, and thus the bioavailability of the new pellets based sachet formulation of esomeprazole is considered to be comparable to the bioavailability of the capsule of esomeprazole 40 mg. The 90% CIs for the ratio (sachet/capsule) of the geometric means for AUC_I were contained in the interval 80-125%. Esomeprazole 40 mg given as a sachet formulation resulted in similar values of t_{max} and $t_{1/2}$ as when given as a capsule.

SUMMARY TABLE OF COMPARATIVE BIOAVAILABILITY DATA
Esomeprazole
(40 mg (Sachet) x 40 mg (capsules))
From measured data
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Esomeprazole DR granules 40 mg Sachet	Esomeprazole 40 mg DR Capsule*	% Ratio of Geometric Means#	Confidence Interval 90% CI#
AUC_T (µmol*h/L)	5.9 7.2 (64.3)	6.0 7.4 (62.9)	98%	93%-103%
AUC_I (µmol*h/L)	6.0 7.4 (65.3)	6.1 7.6 (63.5)	98%	93%-103%
C_{max} (µmol/L)	2.9 3.3 (49.1)	3.2 3.6 (47.3)	90%	84%-96%
T_{max} § (h)	2.00 (1.0-5.0)	2.00 (0.7-4.5)		
$T_{1/2}$ + (h)	1.1 (42.0)	1.1 (36.3)		

* Esomeprazole capsules, AstraZeneca, Sweden
§ Expressed as the median (range) only
+ Expressed as arithmetic mean (CV%) only
# Based on least squares estimates

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamic Data Supporting Oral Clinical Use of Esomeprazole in Adult Patients

Primary Pharmacological Effects

Esomeprazole inhibits the gastric H^+, K^+-ATPase, the enzyme identified as the proton pump of the parietal cell. The effect of esomeprazole on acid formation has been compared to that of the racemate, omeprazole, and the other enantiomer (R-omeprazole) *in vitro*, in isolated rabbit gastric glands and *in vivo* in rats and dog. Esomeprazole was shown to inhibit acid secretion to a similar extent as omeprazole, without any significant differences between the 2 compounds *in vitro*. In *in vivo* studies in rats, the R-enantiomer showed a statistically significantly greater inhibition of acid output than the racemate omeprazole, which in turn had a statistically significantly greater effect than esomeprazole. This pharmacodynamic (PD) difference reflected a corresponding difference in total systemic exposure, in that the AUC for the R-enantiomer>omeprazole>esomeprazole. No differences were noted in either the PD or the pharmacokinetic (PK) *in vivo* data in dogs. Thus, the pharmacodynamic effects of esomeprazole and omeprazole are similar at equivalent systemic exposure, and therefore, the PD studies performed with omeprazole can also be considered relevant for esomeprazole.

Omeprazole had a long duration of action in all species studied. Repeated daily doses resulted in a progressive increase in the antisecretory effect during the first 3-5 days of administration. In dogs, a dose of 0.5 μmol/kg (given as enteric coated granules) inhibited histamine-stimulated gastric acid secretion by about 20% when measured 24 hours after the first dose, and by 60-65% when measured 24 hours after dosing at steady state. Once steady-state conditions were reached (after 3-5 days), acid inhibition remained unchanged, as established in dogs treated for periods of up to one year.

Acid secretion recovers after discontinuation of long-term treatment at the same rate as after a single dose of omeprazole, in parallel with the recovery of H^+, K^+-ATPase activity in the oxyntic mucosa. Whether this recovery reflects de novo synthesis of the H^+, K^+-ATPase molecules or the dissociation of the inhibitor from the enzyme has not yet been established.

Due to the potency and long duration of action of esomeprazole, repeated administrations of high doses in the rat resulted in a marked decrease of acid secretion and a secondary hypergastrinemia and hyperplasia of G-cells. In rats, administration of esomeprazole 14-140 mg/kg/day resulted in plasma gastrin levels of 140-2400 pg/mL as compared to 75-100 pg/mL in controls. In dogs, high doses of esomeprazole (28 mg/kg/day) produced hypergastrinemia (170-700 pg/mL after food intake), as compared to 53±16 pg/mL in controls. However, no hyperplasia of G-cells was evident in this species.

Secondary Pharmacological Effects

Due to the unique mechanism and specific effect on acid secretion, omeprazole has no significant pharmacodynamic effects unrelated to the inhibition of acid secretion. This property is expected to be shared with esomeprazole.

Mean arterial blood pressure and heart rate in the anesthetized dog were not affected by omeprazole under various challenges. Circulatory and respiratory functions in the dog were not affected by omeprazole, either at rest or during exercise. Omeprazole had no anticholinergic and no antihistamine (H2-receptor) activity. In the rat, no effect on basal locomotor activity nor on exploratory activity was recorded, suggesting that omeprazole is devoid of sedative or neuroleptic effects.

Pharmacodynamic Data Supporting Oral Clinical Use of Esomeprazole in Pediatric Patients

No additional pharmacology studies in juvenile animals were necessary.

Pharmacokinetic Data Supporting Oral Clinical Use of Esomeprazole in Adult Patients

Absorption and Distribution

Absorption of esomeprazole is rapid. Peak plasma levels were found within 5 minutes in the rat following duodenal administration, and within 15 minutes in the dog following oral administration. The bioavailability of esomeprazole (34%) was not significantly different from that of omeprazole (38%) in rats. In dogs, the bioavailability of esomeprazole was higher than that of the other enantiomer. Esomeprazole showed enantiomeric stability, with a maximum of 2% of the other enantiomer detected in blood following a single intraduodenal administration of esomeprazole in rats.

In rats, the AUC for the R-enantiomer>omeprazole>esomeprazole at pharmacologically relevant dose levels. However, the difference was less clear at the high dose levels used in the toxicology studies. Higher plasma concentrations of both esomeprazole and omeprazole were consistently noted in female rats compared to males. Values seen in pregnant rats were of the same order of magnitude as those noted in non-pregnant females. However, exposure in pregnant rabbits after oral administration was relatively low, and thus this species was considered to be less relevant for reproduction toxicity studies on esomeprazole than the rat.

Overall, PK and toxicokinetic (TK) evaluations did not reveal any major differences between esomeprazole and omeprazole with regards to the systemic exposure in dogs. No differences were noted in the C_{max} and AUC values for esomeprazole and omeprazole in dogs at pharmacologically effective doses. At the higher dose levels used in the toxicity studies, the C_{max} of esomeprazole tended to be somewhat higher after administration of the same oral dose, but the exposure (AUC) was equivalent. No differences were seen between male and female dogs.

After absorption, omeprazole and esomeprazole are rapidly distributed to extravascular sites, and about 85%-90% is bound to plasma proteins. The distribution of 14C-labelled omeprazole in the mouse was investigated by autoradiography. Radioactivity was initially found in the blood and most organs. Sixteen hours after administration, the drug was confined predominantly to the stomach wall. At 48 hours, the radioactivity was eliminated.

Penetration of omeprazole and/or its metabolites across the blood-brain and placental barriers was low.

Metabolism and Excretion

The in vitro metabolic disposition of esomeprazole was compared with that of omeprazole in liver microsomal preparations from adult mice, rats, rabbits, dogs and humans. The main metabolites formed did not indicate major differences in the qualitative metabolic disposition between esomeprazole and omeprazole, with respect to species, sex or the structure of metabolites formed.

The excretion and metabolism of esomeprazole was compared to that of omeprazole *in vivo*, in dogs, following oral administration. Extensive metabolism was confirmed with similar excretion patterns in the urine and feces and with the same pattern of metabolites. All the major metabolites identified following the administration of omeprazole were also found after administration of esomeprazole. Identifiable metabolites constituted about 54% of the total metabolite excretion in 10 hours, and about 12% of the administered dose. There are no differences in excretion routes and recovery between esomeprazole and omeprazole after oral administration to dogs.

Pharmacokinetic Data Supporting Clinical Use of Esomeprazole in Pediatric Patients

The plasma protein binding levels for esomeprazole were similar (about 90%) in neonatal, juvenile and young adult rats. The degree of binding in dogs was about 85% to 90%, and again did not seem to vary with age.

In juvenile rats and dogs, the exposure to esomeprazole was generally comparable between males and females, although there was a slight tendency towards a higher exposure in female than in male rats at the highest dose level on Dose Day 28. The C_{max} for esomeprazole was observed between 10 and 60 minutes in juvenile rats and generally at 20 minutes for juvenile dogs. The exposure generally increased more than proportionally to the increase in dose in both juvenile rats and dogs.

The AUC for esomeprazole and omeprazole in juvenile rats and for esomeprazole in juvenile dogs decreased notably with the duration of treatment and/or the age of the animals, resulting in 10-fold lower AUC values after 1 month's once-daily treatment in rats or 2 or 3 months' once-daily treatment in dogs, compared to Dose Day 1. The decrease in exposure in dogs was similar, regardless of whether esomeprazole was given once daily or intermittently, once every 14 days. However, when the esomeprazole dosage was increased from once to twice daily dosing from Dose Day 28, both the AUC and C_{max} following the second daily dose were higher

than the values following the first daily dose, on most sampling occasions. Thus, administration of the 2nd dose resulted in a more than dose-proportional increase in exposure, and also AUC values that were only 3-fold lower on Dose Day 91 compared to Dose Day 1. Thus, increasing the dose from once to twice daily administration of esomeprazole from Dose Day 28 resulted in an exposure on Dose Day 91 that was about 5-fold higher than that attained following once daily administration throughout the study.

An investigation of 6 CYP isoenzyme-specific activities in liver microsomes from juvenile and young adult dogs showed some increase in the activity of EROD (reflecting CYP1A1/2 activity) and also a slight increase in the activity of CZXH (reflecting CYP2E1 activity), after esomeprazole treatment, compared to vehicle-treated animals. However, other CYP isoform activities decreased or were unaffected, and similar changes were seen in both the puppies and young adult dogs treated with esomeprazole once - or twice daily or only intermittently (once every 14 days). In addition, the *in vitro* intrinsic clearance-rate, half-life and metabolic profiles of esomeprazole in liver microsomes from the dogs were similar, regardless of the gender, treatment/vehicle, dosing regimen or age of the pups. Thus, the increases in EROD and CZXH activities were not reflected in the clearance of esomeprazole in the dog liver microsomes, and it is therefore assumed that the metabolism of esomeprazole is mainly mediated by other CYP isoenzymes.

Human Pharmacology

Pharmacodynamics

When administered once daily for 7 days to healthy subjects defined as extensive metabolizers of omeprazole, 15 mg esomeprazole produced a more pronounced reduction in pentagastrin-stimulated acid output (PAO) compared to a dose of 15 mg omeprazole. The median reduction achieved with esomeprazole treatment was 91% as compared to 64% for omeprazole treatment.

Oral dosing with 5 to 20 mg esomeprazole once daily for 5 days resulted in a rapid and dose-dependent reduction in stimulated gastric acid secretion in healthy subjects.

Table 15 Percent Inhibition (Estimates and 95% CIs) Following Single and Repeated Doses of Esomeprazole DR tablets or Omeprazole.

	Mean % Inhibition of PAO Estimate (95% CI)	
	Single Dose	**Repeated Doses**
esomeprazole, 5 mg	14.6	27.8
esomeprazole, 10 mg	29.2	62.1
esomeprazole, 20 mg	45.7	89.9
omeprazole, 20 mg	35.4	78.7

In a three-way cross-over study of 36 male and female patients with heartburn and acid regurgitation (symptoms of GERD), esomeprazole delayed release tablets 20 and 40 mg had a dose-

dependent effect on intragastric acidity that was significantly greater than that seen with treatment with 20 mg omeprazole, following daily dosing for 5 days (see table below).

Table 16 Percentage of Patients With Intragastric pH >4 Following Repeated Dosing (5 days) With Esomeprazole Magnesium DR Tablets or Omeprazole (n=36).

Treatment	Percentage of Patients with Intragastric pH >4	
	At Least 12 h	At Least 16 h
Esomeprazole DR tablets 40 mg	92%	56%
Esomeprazole DR tablets 20 mg	54%	24%
omeprazole 20 mg	45%	14%

A similar study (two-way cross-over design) was also undertaken in 115 male and female patients with symptoms of GERD to compare the effects of daily doses of esomeprazole delayed release tablets 40 mg versus omeprazole 40 mg on intragastric acidity. The results of this study demonstrated that esomeprazole delayed release tablets 40 mg resulted in a significantly greater proportion of time with intragastric pH>4 than omeprazole 40 mg after both one and five days ($p<0.001$).

Table 17 Percentage of Patients With Intragastric pH >4 Following Repeated Dosing (5 days) With Esomeprazole DR tablets or Omeprazole (n=115).

Treatment	Percentage of Patients with Intragastric pH >4	
	At Least 12 h	At Least 16 h
Esomeprazole DR tablets 40 mg	88%	56%
omeprazole 40 mg	77%	45%

In a two-way cross-over study of 31 male and female patients with heartburn and acid regurgitation (symptoms of GERD), daily doses of esomeprazole delayed release tablets 40 mg resulted in a significantly greater proportion of time with intragastric pH>4 than daily pantoprazole 40 mg after both one and five days ($p<0.001$).

Table 18 Percentage of Patients With Intragastric pH >4 Following Repeated Dosing (5 days) With Esomeprazole DR tablets or Pantoprazole (n=31).

Treatment	Percentage of Patients with Intragastric pH >4	
	At Least 12 h	At Least 16 h
Esomeprazole DR tablets 40 mg	90%	50%
pantoprazole 40 mg	30%	10%

In a two-way cross-over study of 30 male and female healthy volunteers, daily doses of esomeprazole delayed release tablets 40 mg resulted in a significantly greater proportion of time with intragastric pH>4 than daily 30 mg lansoprazole after five days ($p<0.001$).

Table 19 Percentage of Subjects With Intragastric pH >4 Following Repeated Dosing (5 days) With Esomeprazole DR Tablets or Lansoprazole (n=30).

Treatment	Percentage of Subjects with Intragastric pH >4	
	At Least 12 h	At Least 16 h
Esomeprazole DR tablets 40 mg	90%	38%
lansoprazole 30 mg	57%	5%

Other Pharmacodynamic Effects

The effect of esomeprazole on various organ systems has not been investigated. Data taken from clinical studies using omeprazole capsules show that no clinically significant effects attributable to the drug could be found for the following parameters: Endocrine: plasma levels of insulin, C-peptide, glucagon, PTH, thyroid hormones or sex hormones, basal levels of cortisol; Cardiovascular: blood pressure, heart rate, electrocardiogram; Renal: renal handling of acid and electrolytes; Hepatic: liver enzymes. However, in some patients receiving esomeprazole, elevated concentrations of alkaline phosphatase, S-ASAT and S-ALAT have been reported.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long term treatment with esomeprazole. The findings are considered to be of no clinical significance.

No clinically significant CNS effects have been recorded.

No clinically significant effects on other organ systems have been noted.

Pharmacokinetics

Esomeprazole undergoes first-pass metabolism, and is completely metabolized by the cytochrome P-450 system (CYP), mainly in the liver. Its metabolism is dependent upon the polymorphically expressed, specific isoform, CYP 2C19 (S-mephenytoin hydroxylase) and CYP 3A4. Less individual variability is seen in the pharmacokinetics of esomeprazole as compared to omeprazole. The influence of CYP 2C19 polymorphism is also less pronounced for esomeprazole than for omeprazole.

Nine major urinary metabolites have been detected. The two main metabolites have been identified as hydroxyesomeprazole and the corresponding carboxylic acid. Three major metabolites have been identified in plasma: the 5-O-desmethyl- and sulphone derivatives and hydroxyesomeprazole. The major metabolites of esomeprazole have no effect on gastric acid secretion.

Please refer to ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics and DRUG INTERACTIONS for the results of pharmacokinetic studies in special populations and drug interaction studies**.**

TOXICOLOGY

Toxicology Data Supporting the Oral Use of Esomeprazole in Adult Patients

Single-dose Toxicity

Table 20 Single-dose Toxicity Studies of Esomeprazole.

Species	Sex	Route	Min. Lethal Dose (mg/kg)	Max. Non-Lethal Dose (mg/kg)
Rat	M	p.o.[1]	930	480
	F	p.o.[1]	480	240
Rat	M	i.v.[2]	290	170
	F	i.v.[2]	290	170

[1] aqueous solution, [2] solution in physiological saline

The single dose toxicity of esomeprazole was studied in Wistar rats following oral and i.v. administration and compared to that of omeprazole. The effects of esomeprazole, administered either intravenously or orally, were similar to those previously reported for omeprazole. A small but clear difference in response between the sexes was seen.

The main signs of acute toxicity were reduced motor activity, coupled with changes in respiratory frequency and abdominal respiration. Intermittent clonic convulsions, sometimes associated with dyspnea, increased salivation, cyanosis, tremor, ataxia and/or very reduced motor activity were also seen. Death occurred within 23 hours of oral treatment or 2 hours of i.v. administration.

Repeat-dose Toxicity

The repeat-dose toxicity of esomeprazole was studied in rats (Wistar and Sprague-Dawley) and dogs after oral administration. Rats received oral doses of 14-280 mg/kg, and dogs 0.66-28 mg/kg, for up to 3 months. Esomeprazole has a low systemic toxicity. Some slight haematological changes indicating a mild microcytic, hypochromic anaemia (possibly due to an iron deficiency) were observed in adult rats, following repeat-dose oral treatment with high doses of esomeprazole or omeprazole. Similar slight changes were seen in pregnant rabbits, but no such changes were noted in esomeprazole-treated dogs. In both rats and dogs, histopathological changes in the stomach at the intermediate and high dose levels (rats: 69 and 280 mg/kg; dogs: 5.5 and 28 mg/kg) consisting of dose-dependent chief cell atrophy, mucosal hyperplasia, and/or focal necrosis of gastric glands, were accompanied by a dose-dependent increase in stomach weight and serum gastrin levels. These changes were expected and consistent with previous observations following treatment with high doses of omeprazole. These effects are the results of gastrin stimulation and/or inhibition of gastric acid secretion.

Reproduction Studies

Slight maternal toxicity was noted in pregnant rats treated orally with esomeprazole or omeprazole at doses of up to 280 mg/kg/day, but no adverse effects could be detected on

embryo-foetal survival or development. The systemic exposure to esomeprazole in these animals was substantially higher than that seen in the clinical situation, indicating an adequate margin of safety.

Neither did treatment of pregnant rabbits with esomeprazole or omeprazole indicate any potential for disturbance of embryo-foetal development. However, severe and dose-related maternal toxicity was noted at relatively low doses and exposure of esomeprazole/omeprazole, resulting in some minor litter effects (a slight reduction in fetal weight and a small increase in the incidence of minor skeletal defects at doses of 26 and 86 mg/kg/day). Although exposure to esomeprazole was relatively low in many of the does, the highest dose level used could not be increased due to this maternal toxicity.

Mutagenicity

Esomeprazole was not mutagenic in an *in vitro* Ames Salmonella test, but was clastogenic in an *in vitro* chromosome aberration test in peripheral human lymphocytes. When compared head to head in another study in peripheral human lymphocytes, esomeprazole, omeprazole, the R-enantiomer of omeprazole and lansoprazole induced the same type and degree of chromosome aberrations. Esomeprazole did not show any evidence of mutagenic potential *in vivo* in a mouse micronucleus test or in a chromosome aberration test in rat bone marrow in spite of extensive exposure.

Carcinogenicity

An 18-month oral study was conducted in mice at doses of 14, 44 and 140 mg/kg/day of omeprazole. No evidence of carcinogenic potential was seen. A 24-month oral study was conducted in rats at doses of 14, 44 and 140 mg/kg/day. No increase in carcinomas was observed in any organ. However, there were dose- and time-dependent increases of tumour-like proliferations in the stomach. Histology showed a continuum from diffuse ECL-cell hyperplasia in the basal region of the gastric glands to less frequent micronoduli and occasional tumour-like proliferations, some extending into the sub-mucosa. The proliferations were classified as gastric carcinoids. The proliferation of ECL-cells and development of carcinoids were more frequent in female rats. No metastases were identified in any of the animals. Carcinoids have not been observed after long-term administration of omeprazole to mice and dogs.

Gastric ECL-Cell Carcinoids

Extensive investigations have been carried out to explain the ECL-cell hyperplasia and the gastric carcinoid findings in rats. In one series of experiments, the antrum of rats was surgically excluded from the rest of the stomach. The removal of acid from the antrum in this way led to pronounced hypergastrinemia and, secondary to this, gastric ECL-cell proliferation. Antrectomy, which removes the source of gastrin, led to hypogastrinemia and a decrease in gastric ECL-cell density. These experiments indicated that gastrin has a direct trophic effect on gastric ECL-cells. In another series of experiments, high doses of omeprazole and a histamine H2-receptor blocker caused hypergastrinemia and increased ECL-cell density. In

antrectomized rats given a high dose of omeprazole, plasma gastrin levels remained normal, and consequently there was no increase in ECL-cell density. It has therefore been concluded that (i) inhibition of gastric acid secretion by large doses of omeprazole or a histamine H2-receptor blocker evokes a natural feedback response leading to hypergastrinemia, (ii) long-standing hypergastrinemia leads to gastric ECL-cell proliferation, and (iii) there is no direct trophic effect of omeprazole on gastric ECL-cells.

An additional long-term (24 months) toxicity study of omeprazole in female rats (1.8-14 mg/kg/day) confirmed that the ECL-cell carcinoids were extreme end-life tumours and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8-140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found, and the ECL-cell hyperplasia seen after 12 months recovered to normal during the next 12 months of no treatment.

No carcinoids were found in the mice carcinogenicity study over 18 months, in a 6-month carcinogenicity bioassay conducted with omeprazole in p53± heterozygous and C57BL/6 (background strain) mice at dose levels of up to 830 mg/kg/day, or in dogs following administration of 0.17 mg/kg/day omeprazole for 7 years.

Treatment with esomeprazole delayed release tablets for up to 1 year in more than 800 patients resulted in moderate increases in serum gastrin levels. However, no significant pathological changes in the gastric oxyntic endocrine cells were observed.

Toxicology Data Supporting the Oral Use of Esomeprazole in the Pediatric Population

There was no unexpected toxicity and/or other effects following esomeprazole treatment of rats or dogs from the neonatal period, during suckling and beyond weaning, compared to those previously observed in adult animals.

CNS signs and mortality were noted at the beginning of the dosing period at the highest esomeprazole dose levels in both neonatal/juvenile rats and dogs. This effect can be attributed to the high esomeprazole plasma levels attained in this age of animal. These plasma levels were within the range at which CNS signs (but not mortality) have previously been seen in adult animals, but additional effects such as repeated dehydration/starvation in the affected neonatal animals probably also contributed to the poor general condition and mortality in these young individuals.

As in the adult rats and pregnant rabbits, a mild microcytic, hypochromic anaemia (which was probably due to an iron deficiency) was observed in both the esomeprazole-treated juvenile rats and dogs. This reaction was more pronounced in the young animals compared to that seen previously in adult animals, was shown to be dose- and time-related, and was fully reversible by the end of the dose-free recovery period.

The low level of changes in the number of ECL-cells in the gastric mucosa that were seen in both the juvenile rats and dogs, and the complete lack of other gastric histopathological changes, indicate that neonatal/juvenile rats and dogs are not more susceptible to proliferative

changes in the gastric mucosa following esomeprazole treatment, compared to adult animals.

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[Pr]Nexium® Product Monograph. Control No. 207636, Date of Revision: November 27, 2017, AstraZeneca Canada Inc.

PART III
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]MYLAN-ESOMEPRAZOLE

Esomeprazole Delayed Release Tablets

Read this carefully before you start taking **MYLAN-ESOMEPRAZOLE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MYLAN-ESOMEPRAZOLE**.

What is MYLAN-ESOMEPRAZOLE used for?
MYLAN-ESOMEPRAZOLE is used in adults to treat problems caused by too much acid in the stomach such as:

- reflux esophagitis (tissue damage caused by the stomach acid and juices moving up the food tube).
- symptoms of reflux disease (e.g. heartburn, backup of stomach contents to the throat).
- duodenal ulcers (sores on the first part of the intestine) caused by a bacterium, *Helicobacter pylori*.
- symptoms of nonerosive reflux disease (NERD), not related to tissue damage of the food pipe such as:
  - a burning feeling that moves up the food pipe (heartburn).
  - a sour or bitter taste moving up to the mouth.
- a rare condition where the stomach produces too much acid (Zollinger-Ellison syndrome).
- ulcers caused by nonsteroidal anti-inflammatory drugs (drugs for pain and sore joints).

MYLAN-ESOMEPRAZOLE is used in children 1-17 years old to treat:

- reflux esophagitis (tissue damage caused by the stomach acid and juices moving up the food tube).
- symptoms of reflux disease (e.g. heartburn, backup of stomach contents to the throat).
- symptoms of nonerosive reflux disease (NERD), not related to tissue damage of the food pipe such as:
  - a burning feeling that moves up the food pipe (heartburn).
  - a sour or bitter taste moving up to the mouth.

How does MYLAN-ESOMEPRAZOLE work?
MYLAN-ESOMEPRAZOLE is a medicine called a proton pump inhibitor (PPI). MYLAN-ESOMEPRAZOLE works by causing less acid to be made in your stomach.

What are the ingredients in MYLAN-ESOMEPRAZOLE?
Medicinal ingredients: esomeprazole magnesium trihydrate

Non-Medicinal ingredients:
Each MYLAN-ESOMEPRAZOLE tablet contains the following non-medicinal ingredients (listed in alphabetical order): cellulose microcrystalline, crospovidone, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, iron oxide, magnesium stearate, methacrylic acid ethylacrylate copolymer, polyethylene glycol, polysorbate, synthetic paraffin, sodium stearyl fumarate, sugar spheres, talc, titanium dioxide, triethyl citrate.

MYLAN-ESOMEPRAZOLE comes in the following dosage forms:
MYLAN-ESOMEPRAZOLE 20 mg tablets are available in HDPE bottles of 100 tablets.
MYLAN-ESOMEPRAZOLE 40 mg tablets is available in HDPE bottles of 100 tablets**.**

Do not use MYLAN-ESOMEPRAZOLE if:
- you are allergic to the active ingredient esomeprazole, substituted benzimidazoles or any of the other ingredients of MYLAN-ESOMEPRAZOLE (see **What are the ingredients in MYLAN-ESOMEPRAZOLE**). If you think you may be allergic, ask your doctor for advice.
- you are taking rilpivirine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MYLAN-ESOMEPRAZOLE. Talk about any health conditions or problems you may have, including if you:
- have had any health problems in the past.
- have symptoms that may be a sign of a more serious problem in your stomach or intestine such as:
  - trouble swallowing.
  - unplanned weight loss.
  - vomiting blood or food.
  - black (blood-stained) stools.
- are pregnant or trying to become pregnant.
- are breastfeeding or planning to breastfeed.
- are due to have a specific blood test (Chromogranin A).

Other warnings you should know about:
MYLAN-ESOMEPRAZOLE is not recommended for use in patients under 1 year of age.

This medicine should be used at the lowest dose and for the shortest time suitable for your condition. Talk to your doctor if you have any concerns about your treatment.

Treatment in combination with antibiotics:
If you experience symptoms such as severe (bloody or repeated watery) diarrhea, with or without fever, abdominal pain or tenderness, you may have bowel inflammation caused by a bacterial infection (*Clostridium difficile*). If this happens, stop taking the drug combination and call your healthcare professional immediately.

Long-term use of PPIs may interfere with the absorption of Vitamin B12 from the diet. This may cause a shortage of Vitamin B12 in your body. Talk to your doctor about this risk.

Long-term use of PPIs may lead to low blood magnesium in some people. When blood magnesium is lower than normal, it may also lead to low blood calcium and low blood potassium.

Using PPIs for a long time (every day for a year or longer) may increase risks of broken bones of the hip, wrist or spine. Talk to your doctor about this risk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MYLAN-ESOMEPRAZOLE:

- drugs used to prevent blood clotting (warfarin or coumarin derivatives, clopidogrel). Speak to your doctor or pharmacist if you are taking any of these drugs. Use of MYLAN-ESOMEPRAZOLE with clopidogrel should be avoided.
- medication for HIV: MYLAN-ESOMEPRAZOLE may decrease the effectiveness of some drugs used for HIV treatment; atazanavir, nelfinavir, and saquinavir should not be used with MYLAN-ESOMEPRAZOLE.
- a high dose of methotrexate (a drug used in high doses to treat cancer): MYLAN-ESOMEPRAZOLE may need to be temporarily withdrawn.
- Blood levels of some drugs may be influenced if MYLAN-ESOMEPRAZOLE is taken at the same time as drugs used to prevent fungal infections (itraconazole, ketoconazole, voriconazole), anxiety (diazepam), epilepsy (phenytoin), drugs to speed up stomach emptying (cisapride*), transplant rejection (tacrolimus), poor circulation in the legs (cilostazol*), heart problems (digoxin), treatment for tuberculosis (rifampin), St John's Wort (*Hypericum perforatum*) or a certain type of anticancer drug (erlotinib or any other anticancer drug from the same class). However, none of these interactions have been shown to change the effectiveness of MYLAN-ESOMEPRAZOLE or the other drug.

Drug interactions can be different if you take MYLAN-ESOMEPRAZOLE for short periods of time than if you take it every day.

*not marketed in Canada

How to take MYLAN-ESOMEPRAZOLE:
Follow your doctor's directions carefully. They may be different from the information contained in this leaflet.

- Take all doses of MYLAN-ESOMEPRAZOLE that your doctor prescribes even when you or your child feel well. In some cases, doses every day are needed to control pain and symptoms, to correct acid problems and to help damaged areas heal.
- If you take MYLAN-ESOMEPRAZOLE with antibiotic drugs, it is important that you take all medications twice each day. Take them at the right time each day for one week. Studies have shown that patients who take their medications as prescribed have better ulcer healing rates and greater success getting rid of their *H. pylori* infection.

- Take MYLAN-ESOMEPRAZOLE until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if MYLAN-ESOMEPRAZOLE is stopped too soon.

MYLAN-ESOMEPRAZOLE needs to be taken for the full treatment duration to help correct acid problems.
- MYLAN-ESOMEPRAZOLE may be taken with food or on an empty stomach.

Tablets:
The tablet may be swallowed whole with water. It may also be put in half a glass of water where it will break apart. This will make it easier to swallow. Be sure to swallow all the tiny pellets that come out of the tablet without chewing them. Don't let the pellets sit in water for more than 30 minutes before drinking them. After drinking, rinse the glass with water and drink this as well.

Usual dose:
Adults
Your doctor may tell you to take MYLAN-ESOMEPRAZOLE:
- 20 to 40 mg once a day for 2 to 8 weeks.
- Continue taking MYLAN-ESOMEPRAZOLE 20 mg each day. This is to keep your symptoms from coming back.
- In combination with antibiotic drugs for one week to treat ulcers caused by *Helicobacter pylori*. This also helps to reduce the risk of these ulcers from coming back.
  - Your pharmacist should also give you information on the two antibiotics.

Maintenance Treatment of NERD (on-demand) dose
After first treatment of NERD, your doctor may suggest that you take MYLAN-ESOMEPRAZOLE 20 mg once daily, as needed, if symptoms of heartburn and regurgitation return once in a while. Contact your doctor if your symptoms get worse, won't go away, or if new symptoms arise.

Children (1 – 11 years of age)
The suggested dose for treating acute disease is 20 mg once daily for 8 weeks.

Children (12 –17 years of age)
The suggested dose for treating acute disease is 20 or 40 mg once a day for 2 to 8 weeks.

To treat ulcers caused by *Helicobacter pylori* in adults, take one 20 mg tablet twice a day.

Overdose:

If you think you have taken too much MYLAN-ESOMEPRAZOLE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you/your child miss a dose of MYLAN-ESOMEPRAZOLE, and remember within 12 hours, take the tablet as soon as possible. Then go back to the regular schedule. If more than 12 hours have passed, do not take the missed dose. Do not double the dose. Just take the next dose on time.

What are possible side effects from using MYLAN-ESOMEPRAZOLE?

Like all medicines, MYLAN-ESOMEPRAZOLE may cause side effects in some people. Side effects are usually mild. They usually go away a short time after starting MYLAN-ESOMEPRAZOLE.

These are not all the possible side effects you may feel when taking MYLAN-ESOMEPRAZOLE. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions. These side effects may not be caused by MYLAN-ESOMEPRAZOLE in your case, but only a doctor can assess this.

Tell your doctor right away if you have any of these symptoms:

- New or worsening joint pain
- Rash on your cheeks or arms that gets worse in the sun

If these side effects become bothersome (or last longer than 1-2 days), discuss with your doctor:
Common:

- Nausea.
- Stomach upset.
- Diarrhea.
- Headache.

Uncommon:

- Dry mouth.
- Dizziness.
- Insomnia.
- Feeling of burning/prickliness/numbing.
- Swelling of extremities.
- Feeling sleepy.
- Feeling like you or your surroundings are moving (vertigo).

Rare:

- Taste disorders.
- Nervousness.
- Hair loss.
- Increased sweating.

Stopping your PPI therapy after taking it for a long time may cause your symptoms to get worse and your stomach may increase acid production. Carefully follow your doctor's instructions when stopping MYLAN-ESOMEPRAZOLE.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE (≥ 1 in 10 000 patients but < 1 in 1000 patients)			
skin reactions (such as rash, dermatitis, itching and/or hives)		X	
blurred vision		X	
depression		X	
confusion		X	
shortness of breath		X	
inflammation in the mouth		X	
severe allergic reaction (such as swelling or anaphylactic reaction/shock)			X
muscle pain		X	
blood disorders (reduced number of cells in the blood, low blood sodium[θ])		X	
inflammation of liver (skin and eyes appear yellow)			X
gastrointestinal fungal infection		X	
photosensitivity		X	
sore joints		X	
feeling ill		X	
VERY RARE (< 1 in 10 000 patients)			
severe skin disorders (blisters, ulcers and/or lesions)			X
aggression		X	
hallucinations		X	
severely impaired liver function		X	
decreased consciousness		X	
inflammation of the kidney		X	
muscular weakness		X	
development of breasts in males		X	
low blood magnesium[θ] (which may result in low blood calcium and/or low blood potassium)		X	
Inflammation in the gut (leading to diarrhea)		X	

[θ] These would only be seen if a blood test was taken.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep MYLAN-ESOMEPRAZOLE well out of reach of children.
- Keep MYLAN-ESOMEPRAZOLE at room temperature (15-30°C).
- Do not keep MYLAN-ESOMEPRAZOLE in the bathroom medicine cabinet or other warm, moist places.
- Do not use MYLAN-ESOMEPRAZOLE after the expiry date marked on the pack.

Keep out of sight and reach of children.

If you want more information about MYLAN-ESOMEPRAZOLE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; or by calling 1-800-575-1379
- This document can be found at: www.mylan.ca.

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