PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}pms-ESOMEPRAZOLE DR

Esomeprazole Magnesium Delayed Release Capsules

Delayed-Release Capsules, 20 mg, 40 mg esomeprazole (as esomeprazole magnesium dihydrate), Oral

H^+, K^+-ATPase Inhibitor

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-ESOMEPRAZOLE DR (esomeprazole magnesium delayed-release capsules) is indicated in adults (18 years of age and above) 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. pylor*i) eradication

pms-ESOMEPRAZOLE DR, 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 magnesium 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 analyzed in this subgroup (see Table 15).

1.1 Pediatrics

pms-ESOMEPRAZOLE DR IS NOT RECOMMENDED FOR USE IN CHILDREN UNDER 12 YEARS OF AGE.

Pediatrics (12-17 years of age)
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of esomeprazole magnesium in pediatric patients has been established. Therefore, Health Canada has authorized the following indication for pediatric use. pms-ESOMEPRAZOLE DR 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)

2 CONTRAINDICATIONS

pms-ESOMEPRAZOLE DR is contraindicated:

- in patients who are hypersensitive to esomeprazole magnesium, substituted benzimidazoles or to any ingredient in the formulation, including any non-medicinal ingredient, or

component of the

container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, 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
- with co-administration of rilpivirine due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see General; and 9.4 Drug-Drug Interactions)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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).

4.2 Recommended Dose and Dosage Adjustment

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

Adults

Reflux Esophagitis: The recommended dose in patients with reflux esophagitis is 40 mg pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR 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 14 CLINICAL TRIALS, In Patients with Zollinger-Ellison Syndrome - Trial Design and Study Demographics; and Study Results). 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 pms-ESOMEPRAZOLE DR 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days. No further treatment with pms-ESOMEPRAZOLE DR is required to ensure healing and/or symptom control.

In Patients with a History of Duodenal Ulcer: The recommended dose is pms-ESOMEPRAZOLE DR 20 mg, amoxicillin 1,000 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 (12-17 years of age)
pms-ESOMEPRAZOLE DR IS NOT RECOMMENDED FOR USE IN CHILDREN UNDER 12 YEARS OF AGE.

No dose adjustment is required for children 12 to 17 years of age (see 7.1.3 Pediatrics; and 10.3 Pharmacokinetics).

Reflux Esophagitis:
The recommended dose in pediatric patients (12-17 years of age) with reflux esophagitis is 20 mg or 40 mg pms-ESOMEPRAZOLE DR once daily for 4 to 8 weeks.

Nonerosive Reflux Disease (NERD): In pediatric patients (12-17 years of age) with heartburn and/or acid regurgitation, without esophagitis, the recommended dose is 20 mg pms-ESOMEPRAZOLE DR once daily for 2 to 4 weeks. If symptom control is not achieved after 4 weeks of treatment, further investigation is recommended.

Special Populations
Patients with Renal Insufficiency: No dose adjustment is required (see Renal).

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 Hepatic/Biliary/Pancreatic).

Elderly Patients: No dose adjustment is required (see 7.1.4 Geriatrics).

Genetic Polymorphism: Dosage adjustment of pms-ESOMEPRAZOLE DR based on CYP 2C19 status is not necessary. See Endocrine and Metabolism; and 10.3 Pharmacokinetics.

Sex
Dosage adjustment based on gender is not necessary. See 10.3 Pharmacokinetics.

4.4 Administration

DO NOT administer via naso-gastric feeding tubes.

The capsules should be swallowed whole with sufficient water. DO NOT crush or chew the capsules.

The capsules may also be opened and the granules inside carefully emptied in half a glass of non-carbonated water. No other liquids should be used as the enteric coating of the granules may be dissolved. Stir and drink the liquid with the granules immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The granules must not be chewed or crushed.

4.5 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.

5 OVERDOSAGE

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 magnesium (280 mg), demonstrated symptoms that were transient, and included weakness, loose stools and nausea. Single doses of 80 mg esomeprazole magnesium 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 16 NON-CLINICAL TOXICOLOGY).

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Capsule / 20 mg and 40 mg esomeprazole magnesium	Diacetylated Monoglycerides, Dimethicone Emulsion, Hydroxypropyl Methylcellulose, Mannitol, Methacrylic Acid-Ethyl Acrylate Copolymer (1:1) Dispersion 30%, Polysorbate 80, Stearyl Macrogolglycerides, Sugar Spheres, Talc, Triethyl Citrate. The capsule shell is composed of Gelatin, Titanium Dioxide and Yellow Iron Oxide. The Black Ink is composed of Black Iron Oxide, Butyl Alcohol, Dehydrated Alcohol, Isopropyl Alcohol, Potassium Hydroxide, Propylene Glycol, Purified Water, Shellac, Strong Ammonia.

Dosage Forms and Packaging

20 mg: Hard gelatin capsules, ink-printed in black with "20 mg" on the opaque yellow cap and "20 mg" on the opaque white body.

40 mg: Yellow, opaque, hard gelatin capsules, ink-printed in black with "40 mg" on the cap and "40 mg" on the body.

The 20 mg capsules are provided in HDPE bottles of 100 capsules and press-through blister strips in cartons of 30 capsules.

The 40 mg capsules are provided in HDPE bottles of 100 capsules and press-through blister strips in cartons of 30 capsules.

7 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:

pms-ESOMEPRAZOLE DR is indicated in combination with antibiotics for the treatment of duodenal ulcer disease and eradication of *Helicobacter Pylori*. One of the recommended antibiotics, clarithromycin, should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy. Refer to the Product Monograph for clarithromycin before using the product (see 7.1.1 Pregnant Women).

Pseudomembranous Colitis:

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, which are used together with proton pump inhibitors (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 PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPI's 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 magnesium (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 magnesium and clopidogrel should be avoided (see 9.4 Drug-Drug Interactions).

Concomitant use of 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 9.4 Drug-Drug Interactions).

Concomitant use of 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 2 CONTRAINDICATIONS; and 9.4 Drug-Drug Interactions).
- *Atazanavir and Nelfinavir:* Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see 9.4 Drug-Drug Interactions) (see the atazanavir and nelfinavir Product Monographs).

  If the combination of pms-ESOMEPRAZOLE DR 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 pms-ESOMEPRAZOLE DR should not exceed an equivalent dose omeprazole of 20 mg daily (see atazanavir Product Monograph).

- *Saquinavir:* If pms-ESOMEPRAZOLE DR 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 9.4 Drug-Drug Interactions) (see saquinavir Product Monograph).

Carcinogenesis and Mutagenesis
Treatment with esomeprazole magnesium 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.

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 decreased acid secretion. The effect of esomeprazole magnesium on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months (daily doses of either 20 or 40 mg/day). 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. Prevalence of ECL cell hyperplasia increased with time and dose.

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

Endocrine and Metabolism

Hypomagnesemia, Hypokalemia and Hypocalcemia:

The chronic use of PPIs may lead to hypomagnesemia. 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.

Genetic Polymorphism:

The CYP 2C19 and CYP 3A4 isozymes are responsible for metabolism of esomeprazole magnesium.

CYP 2C19, which is involved in the metabolism of all available PPIs, 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 pms-ESOMEPRAZOLE DR based on CYP 2C19 status is not necessary. See Genetic Polymorphism; and 10.3 Pharmacokinetics).

Gastrointestinal

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with pms-ESOMEPRAZOLE DR is instituted as treatment with pms-ESOMEPRAZOLE DR may alleviate symptoms and delay diagnosis.

withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion. Long-term use of esomeprazole magnesium is associated with an increased risk of fundic gland polyps especially beyond one year (see 8.5 Post-Market Adverse Reactions). Most fundic gland polyps are asymptomatic. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hepatic/Biliary/Pancreatic

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 Gastrointestinal Reflux Disease (GERD) with normal liver function. Metabolism of esomeprazole magnesium 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 magnesium. 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 4.2 Recommended Dose and Dosage Adjustment).

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 pms-ESOMEPRAZOLE DR. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see 8.5 Post-Market Adverse Reactions).

Monitoring and 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, pms-ESOMEPRAZOLE DR treatment should be stopped 14 days before CgA measurements (see 9.7 Drug-Drug Interactions; and 10.2 Pharmacodynamics). The clinical documentation for esomeprazole magnesium does not support the need for routine laboratory monitoring of response to therapy. See Carcinogenesis and Mutagenesis for effects of esomeprazole magnesium on serum gastrin levels and 8.5 Post-Market Adverse Reactions for effects on liver functioning.

Musculoskeletal

Bone Fracture:

Several published observational studies suggest that 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 4 DOSAGE AND ADMINISTRATION; and 8.5 Post-Market Adverse Reactions).

Renal
Since the kidney is responsible for the excretion of metabolites of esomeprazole magnesium but not for the elimination of the parent compound, the metabolism of esomeprazole magnesium 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 4.2 Recommended Dose and Dosage Adjustment).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate or well-controlled studies in pregnant women. Therefore, the safety of esomeprazole magnesium in pregnancy has not been established. pms-ESOMEPRAZOLE DR should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

pms-ESOMEPRAZOLE DR is indicated in combination with antibiotics for the treatment of duodenal ulcer disease and eradication of *Helicobacter Pylori*. One of the recommended antibiotics, clarithromycin, should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy. Refer to the Product Monograph for clarithromycin before using the product.

7.1.2 Breast-feeding

It has not been investigated whether or not esomeprazole magnesium is excreted in human breast milk. No studies in lactating women have been performed. Precaution should be exercised because many drugs can be excreted in human milk. Esomeprazole is the S-isomer of omeprazole, which is secreted in breast milk. Therefore, pms-ESOMEPRAZOLE DR should not be given to nursing mothers unless its use is considered essential.

7.1.3 Pediatrics

Pediatrics (12-17 years of age): The use of esomeprazole magnesium in pediatric patients 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 magnesium for adults, and additionally from b) safety and pharmacokinetic studies performed in pediatric patients (see 8.2.1 Clinical Trial Adverse Reactions – Pediatrics; 10.3 Pharmacokinetics, and in Pediatrics [12-17 years of age]; Study Results).

pms-ESOMEPRAZOLE DR IS NOT RECOMMENDED FOR USE IN CHILDREN UNDER 12 YEARS OF AGE.

Pediatrics (<1 years of age): The safety and effectiveness of esomeprazole magnesium have not yet been established.

7.1.4 Geriatrics

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 magnesium 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 4.2 Recommended Dose and Dosage Adjustment; and 8 ADVERSE REACTIONS.

8 ADVERSE REACTIONS

8.1 Adverse 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 > 8,500 adult patients exposed to esomeprazole magnesium. Additionally, > 1,200 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 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.

8.2 Clinical Trial Adverse Drug Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from

clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adults
The following adverse reactions (>1%), irrespective of causal relationship, were reported in controlled short-term (up to 8 weeks) clinical trials involving 5,668 patients:

Table 2: Adverse Reactions (>1%) Irrespective of Causal Relationship in Short-Term Clinical Trials (up to 8 weeks) Treated with Esomeprazole Magnesium

Adverse Reaction	All Studies	Placebo-Controlled Studies	
	Esomeprazole magnesium 20 and 40 mg n = 5,668 (%)	Esomeprazole magnesium 20 and 40 mg n = 470 (%)	[placebo] n = 240 (%)
Gastrointestinal Disorder			
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	-
Gastritis	2.1	-	-
Constipation	1.6	1.7	1.3
Vomiting	1.4	1.1	1.7
Mouth dry	1.3	1.3	-
Infections and Infestations			
Viral infection	1.1	-	0.4
Nervous System Disorders			
Headache	8.4	6.6	7.5
Dizziness	1.2	0.9	1.7
Respiratory Disorders			
Respiratory infection	3.8	1.9	3.8
Sinusitis	1.7	2.8	2.5
Pharyngitis	1.3	0.4	1.3

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

Table 3: Adverse Reactions (>3%) Irrespective of Causal Relationship in Clinical Trials up to 6 Months Duration Treated with Esomeprazole

Adverse Reaction	Esomeprazole magnesium 10, 20 and 40 mg n = 519 (%)	Placebo n = 169 (%)
Gastrointestinal Disorders		
Diarrhea	6.7	3.0
Gastritis/gastritis aggravated*	6.2	5.3
Flatulence	5.0	1.8
Nausea/nausea aggravated	4.8	2.4
Abdominal pain	3.7	2.4
Vomiting/vomiting aggravated	3.3	1.2
Infections and Infestations		
Viral infection	3.7	1.8
Injury, Poisoning and Procedural Complications		
Accident and/or injury	3.7	1.8
Nervous System Disorders		
Headache	6.6	4.1
Respiratory Disorders		
Respiratory infection	8.5	3.0
Sinusitis	4.2	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 magnesium 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 magnesium 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 pms-ESOMEPRAZOLE DR 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 4: Adverse Reactions (>1%) that Were Assessed by the Investigator to Have a Reasonable Causal Relationship with Treatment in Short-Term Clinical Trials (up to 8 Weeks), for the Healing of Gastric Ulcers Associated with NSAID Therapy

Adverse Reaction	Esomeprazole 20 and 40 mg qd n = 556 (%)	Ranitidine 150 mg bid n = 280 (%)
Gastrointestinal Disorders		
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 events (considered unrelated to esomeprazole magnesium 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 magnesium 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 1,390 patients.

Table 5: Adverse Reactions (>1%) that Were Assessed by the Investigator to Have a Reasonable Causal Relationship with Treatment in Long-Term Clinical Trials (up to 6 Months), for the Risk-Reduction of Gastric Ulcers Associated with NSAID Therapy

Adverse Reaction	Esomeprazole 20 and 40 mg qd n = 936 (%)	Placebo n = 454 (%)
Gastrointestinal Disorders		
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 events (considered unrelated to esomeprazole magnesium 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 e complications.

In addition, the following adverse events of a potentially severe nature (considered unrelated to esomeprazole magnesium 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 magnesium 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, paresthesia, pharyngolaryngeal pain, postoperative pain, proteinuria, pruritus, rhinorrhea.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (12-17 years of age)
In Children (12 – 17 years) with 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.

8.3 Less Common Clinical Trial Adverse Reactions

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

Gastrointestinal disorders: abdominal pain, epigastric pain, gastric retention, gastric ulcer, gastroesophageal reflux, nausea, peptic ulcer aggravated
Investigations: abnormal hepatic function, increased SGOT, increased SGPT, increased phosphatase alkaline
Nervous system disorders: headache, taste perversion
Psychiatric disorders: insomnia

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:

Blood and lymphatic system disorders: anemia, leukopenia, thrombocytopenia
Ear and labyrinth disorders: vertigo
Gastrointestinal disorders: constipation, defecation urge, duodenitis, epigastric pain, eructation, gastric retention, gastric ulcer, dry mouth, mucosal discolouration GI, frequent stools, vomiting
General disorders and administration site conditions: asthenia
Infections and infestations: herpes simplex
Investigations: hepatic enzymes increased NOS, increased SGOT, increased SGPT
Metabolism and nutrition disorders: dehydration, weight decrease, weight increase
Musculoskeletal and connective tissue disorders: back pain
Neoplasms benign, malignant and unspecified (incl cysts and polyps): GI neoplasm
Nervous system disorders: dizziness, headache, hyperesthesia, taste perversion
Psychiatric disorders: anorexia, increased appetite, insomnia, sleep disorder

Skin and subcutaneous tissue disorders: rash

The following adverse reactions occurred for esomeprazole magnesium in clinical trials regardless of studied condition and were considered causally related by the investigator:

Uncommon (<1%)
Skin and subcutaneous tissue disorders: dermatitis, pruritus and urticaria
Nervous system disorders: paresthesia

Rare (<0.1%)
General disorders and administration site conditions: malaise
Metabolism and nutrition disorders: hyponatremia

Very Rare (<0.01%)
Musculoskeletal and connective tissue disorders: muscular weakness
Nervous system disorders: hepatic encephalopathy

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings
For pediatric and adult studies, no clinically important changes or trends were noted over time in clinical chemistry that were different from those already listed under 7 WARNINGS AND PRECAUTIONS, and 8.5 Post-Market Adverse Reactions.

8.5 Post-Market Adverse Reactions

Blood and lymphatic system disorders: Rare reports (<0.1%) of leukopenia and thrombocytopenia; Very rarely (<0.01%) agranulocytosis, pancytopenia

Ear and labyrinth disorders: Uncommon reports (<1%) of vertigo

Eye disorders: Rare reports (<0.1%) of blurred vision

Gastrointestinal disorders: Rare reports (<0.1%) of stomatitis; Very rarely (<0.01%) microscopic colitis Fundic gland polyps (FGPs) (see Gastrointestinal).

General disorders and administration site conditions: Uncommon reports (<1%) of peripheral edema; Rare report (<0.1%) of Malaise

Hepatobiliary disorders: Rare reports (<0.1%) of hepatitis with or without jaundice; Very rarely (<0.01%) hepatic failure

Immune system disorders: Rare reports (<0.1%) of hypersensitivity reactions (e.g., angioedema, anaphylactic reaction/shock)

Infections and infestation: Rare reports (<0.1%) of GI candidiasis

Investigations: Uncommon reports (<1%) of increased liver enzymes

Metabolism and nutrition disorders: Rare reports (<0.1%) of hyponatremia; Very rarely (<0.01%) hypomagnesemia (severe hypomagnesemia may result in hypocalcemia, and hypomagnesemia may also result in hypokalemia)

Musculoskeletal and connective tissue disorders: Rare reports (<0.1%) of myalgia, arthralgia; Very rarely (<0.01%) muscular weakness
Osteoporosis and osteoporosis-related fractures have been reported with multiple daily doses and long-term PPI therapy.

Nervous system disorders: Uncommon reports (<1%) of paresthesia and somnolence; Rare reports (<0.1%) of taste disturbance; Very rarely (<0.01%) hepatic encephalopathy

Psychiatric disorders: Uncommon reports (<1%) of insomnia; Rare reports (<0.1%) of depression, agitation, confusion; Very rarely (<0.01%) aggression, hallucination

Renal and urinary disorders: Very rarely (<0.01%) interstitial nephritis

Reproductive system and breast disorders: Very rarely (<0.01%) gynecomastia

Respiratory, thoracic and mediastinal disorders: Rare reports (<0.1%) of bronchospasm

Skin and subcutaneous tissue disorders: Rare reports (<0.1%) of alopecia, rash, dermatitis, photosensitivity, hyperhidrosis; Very rarely (<0.01%) erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) (some fatal)
Subacute cutaneous lupus erythematosus (SCLE). See Immune.

As of 25 June 2007, 48 medically confirmed case reports have been received 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 magnesium treatment in this age group.

9 DRUG INTERACTIONS

9.2 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 magnesium and diazepam, phenytoin, quinidine or cisapride (not marketed in Canada). Drugs known to inhibit CYP 2C19 or CYP 3A4 or both (such as clarythromycin and voriconazole) may lead to increased esomeprazole magnesium serum levels by decreasing the rate of esomeprazole magnesium'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 magnesium serum levels by increasing the esomeprazole magnesium metabolism.

With on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole magnesium, should be considered when pms-ESOMEPRAZOLE DR is prescribed in this manner (see 4.2 Recommended Dose and Dosage Adjustment).

9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established .

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e.,, those identified as contraindicated).

Diazepam: Concomitant administration of esomeprazole magnesium (30 mg once daily for 5 days) resulted in a 45% decrease in the clearance of diazepam (metabolized by CYP2C19) 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 magnesium (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 (not marketed in Canada): Omeprazole as well as esomeprazole magnesium 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.

Clopidogrel: Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) (metabolized by CYP2C19) and esomeprazole magnesium (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 magnesium, 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 magnesium 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 magnesium + ASA) product groups, likely due to the concomitant administration of low dose ASA (see General).

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

Phenytoin: Concomitant administration of 40 mg esomeprazole magnesium (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 magnesium, 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 General).

Voriconazole: Concomitant administration of esomeprazole magnesium with a combined inhibitor of CYP 2C19 and CYP 3A4, such as voriconazole, may result in more than double the levels of esomeprazole magnesium exposure. Dose adjustment of esomeprazole magnesium is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered.

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 magnesium. The absorption of ketoconazole, itraconazole or erlotinib can decrease during treatment with esomeprazole magnesium.

Digoxin: The absorption of digoxin can increase during treatment with esomeprazole magnesium 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). Therefore, patients may need to be monitored when digoxin is taken concomitantly with pms-ESOMEPRAZOLE DR.

Antiretroviral Drugs
Rilpivirine: Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see 2 CONTRAINDICATIONS; and General).

Atazanavir: Co-administration of pms-ESOMEPRAZOLE DR with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C_{max} and AUC of atazanavir (96% and 94%, respectively, with 40 mg once daily dose of omeprazole) in healthy volunteers administered atazanavir or atazanavir/ritonavir (see General) (see atazanavir Product Monograph).

Nelfinavir: Co-administration of pms-ESOMEPRAZOLE DR with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg once daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and C_{max} for nelfinavir (by 36% and 37%, respectively and its active metabolite M8 (by 92% and 89%, respectively) (see General) (see nelfinavir 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 General) (see the saquinavir Product Monograph). Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1,000/100 mg twice daily) increased saquinavir AUC by 82% and C_{max} by 75%.

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test 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, pms-ESOMEPRAZOLE DR treatment should be stopped 14 days before CgA measurements to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range. (See Monitoring and Laboratory Tests)

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Esomeprazole magnesium delayed-release capsules contain esomeprazole magnesium (the S-isomer of omeprazole). Esomeprazole is acid labile and therefore is administered orally as granules filled into a capsule.

Esomeprazole magnesium (a substituted benzimidazole), reduces gastric acid secretion through a highly targeted mechanism of action. 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 by the parietal cells, thus reducing gastric acidity.
Esomeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion.

10.2 Pharmacodynamics

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 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 6: Effect on Intragastric pH on Day 5 (n = 36)

Parameter	Esomeprazole 40 mg	Esomeprazole 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 magnesium 40 mg vs. esomeprazole magnesium 20 mg

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 magnesium alone has been shown to suppress, but not eradicate *H. pylori.*

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

When administered once daily for 7 days to healthy subjects defined as extensive metabolizers of omeprazole, 15 mg esomeprazole magnesium 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 magnesium treatment was 91% as compared to 64% for omeprazole treatment.

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

Table 7: Percent Inhibition (Estimates and 95% CIs) Following Single and Repeated Doses of Esomeprazole 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 magnesium 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 8: Percentage of Patients with Intragastric pH >4 Following Repeated Dosing (5 days) with Esomeprazole or Omeprazole (n = 36)

Treatment	Percentage of Patients with Intragastric pH >4	
	At Least 12 h	**At Least 16 h**
Esomeprazole 40 mg	92%	56%
Esomeprazole 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 magnesium 40 mg versus omeprazole 40 mg on intragastric acidity. The results of this study demonstrated that esomeprazole magnesium 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 9: Percentage of Patients with Intragastric pH >4 Following Repeated Dosing (5 days) with Esomeprazole or Omeprazole (n = 115)

Treatment	Percentage of Patients with Intragastric pH >4	
	At Least 12 h	**At Least 16 h**
Esomeprazole 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 magnesium 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 10: Percentage of Patients with Intragastric pH >4 Following Repeated Dosing (5 days) with Esomeprazole or Pantoprazole (n = 31)

Treatment	Percentage of Patients with Intragastric pH >4	
	At Least 12 h	At Least 16 h
Esomeprazole 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 magnesium 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 11: Percentage of Subjects with Intragastric pH >4 Following Repeated Dosing (5 days) with Esomeprazole or Lansoprazole (n = 30)

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

Other Pharmacodynamic Effects
In some patients receiving esomeprazole magnesium, elevated concentrations of alkaline phosphatase,
S-ASAT and S-ALAT have been reported.

The findings are considered to be of no clinical significance.

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

10.3 Pharmacokinetics

Table 12: Summary of Esomeprazole Pharmacokinetic Parameters After Oral Administration for 5 Days (%CV)

	C_{max} (mcmol/L)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (mcmol*h/L)
Single dose mean Esomeprazole 20 mg	2.1 (45%)	1.6 (86%)	1.2 (37%)	4.2 (59%)
Single dose mean Esomeprazole 40 mg	4.7 (37%)	1.6 (50%)	1.5 (32%)	12.6 (42%)

Values represent geometric mean except the Tmax, which is the arithmetic mean.

Pharmacokinetics in Combination with Antibiotics
Interactions between esomeprazole magnesium (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 magnesium during concomitant administration with the antibiotic drugs, compared with esomeprazole magnesium alone.

Absorption
Absorption of esomeprazole magnesium in healthy subjects under fasting condition 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 magnesium was studied in 36 patients with NERD after repeated once daily administration of 20 mg and 40 mg.
Food intake delays and decreases the absorption of esomeprazole magnesium although this has no significant influence on the effect of esomeprazole magnesium on intragastric acidity.

Metabolism
Esomeprazole undergoes first-pass metabolism and is completely metabolized by the cytochrome P-450 system, mainly in the liver via CYP 2C19 (S-mephenytoin hydroxylase) and CYP 3A4. The CYP 2C19 isozyme, which is involved in the metabolism of all available proton pump inhibitors, exhibits polymorphism and is less pronounced for esomeprazole magnesium than for omeprazole. 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 magnesium based on CYP 2C19 status is not necessary (see Endocrine and Metabolism; and Genetic Polymorphism).

Almost 80% of an oral dose of esomeprazole magnesium 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. Nine major urinary metabolites have been detected. The two major 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 magnesium have no effect on gastric acid secretion.

In pharmacokinetic studies in experimental animals, including rats, dogs and mice, penetration of omeprazole and/or its metabolites was low across the blood-brain and placental barriers.

Special Populations and Conditions

- **Pediatrics (12-17 years of age)**

Children (12-17 years of age): The pharmacokinetics of esomeprazole magnesium were studied in 28 pediatric patients with GERD aged 12 - 17 years, in a single centre randomized study. Patients received esomeprazole magnesium 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole magnesium 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 magnesium pharmacokinetics in pediatric patients aged 12 - 17 years were similar to those observed in adult patients with NERD.

Table 13: 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 (mcmol*h/L)	3.65	13.86	4.2	12.6
C_{max} (mcmol/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 magnesium is not significantly changed in elderly subjects. Following repeated oral dosing with 40 mg esomeprazole magnesium 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). See 4.2 Recommended Dose and Dosage Adjustment; and 7.1.4 Geriatrics.

- **Sex:** 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. See 4.2 Recommended Dose and Dosage Adjustment.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 25°C. Store in a dry place.

Keep in a safe place out of reach and sight of children.

pms-ESOMEPRAZOLE DR delayed-release capsules are moisture-sensitive. See 12 SPECIAL HANDLING INSTRUCTIONS.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

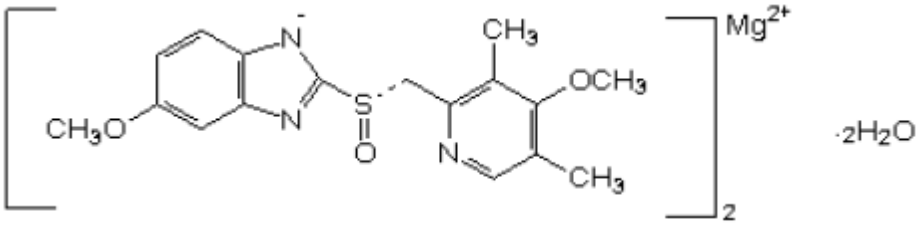
Proper Name: esomeprazole magnesium dihydrate

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

Molecular Formula: $C_{34}H_{36}N_6O_6S_2\ Mg \bullet 2H_2O$

Molecular Mass: 749.2 g/mol (dihydrate)
713.1 g/mol (anhydrous basis)

Structural Formula:



Physicochemical Properties:

Description: Esomeprazole magnesium is a white to slightly coloured crystalline powder, containing two water molecules of hydration.

Solubility: 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.

pKa: The pKa of the benzimidazole (omeprazole base) is 8.8, and that of the pyridinium ion, 4.0.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Reflux Esophagitis

Trial Design and Study Demographics
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.

Study Results
Initial Therapy: 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 (NERD)
Trial Design and Study Demographics
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).

Study Results
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)
Trial Design and Study Demographics
Patients with complete resolution of heartburn following initial treatment for NERD were randomized to double-blind treatment with esomeprazole magnesium 40 mg, 20 mg or placebo, once daily when needed to control symptoms of GERD for 6 months.

Study Results
Time to discontinuation due to unwillingness to continue with current therapy was the primary efficacy variable. Esomeprazole 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 14: 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 40 mg	Esomeprazole 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

Healing of Gastric Ulcers in Patients Requiring NSAID Therapy, Including COX-2 Selective NSAIDs

Trial Design and Study Demographics

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 magnesium (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.

Study Results

In clinical trials, treatment with esomeprazole magnesium (20 mg or 40 mg) once daily was effective, safe and well-tolerated in combination with continuous NSAID use.
Results of the two studies are presented below:

Table 15: 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	91.5	88.4	74.2	85.7	84.8	76.3	88.6	86.6	75.3

	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
weeks (%)									
p-value[a]	<0.001[b]	0.003[b]	-	0.047	0.073	-	<0.001[b]	<0.001[b]	-

E20 = esomeprazole magnesium 20 qd; E40 = esomeprazole magnesium 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 16: 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 magnesium 20 qd; E40 = esomeprazole magnesium 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

Trial Design and Study Demographics
In two large multicentre, randomized, double-blind placebo-controlled trials, esomeprazole magnesium (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 the 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.

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. Study 14 was considered supportive as no ulcer diameter measurements accompanied the qualitative ulcer definition in this trial.

Study Results
In clinical trials, treatment with esomeprazole magnesium (20 mg or 40 mg) once daily was effective, safe and well-tolerated in combination with continuous NSAID use.
Patients treated with esomeprazole magnesium 40 mg or 20 mg had significantly higher estimated ulcer-free rates compared to placebo as shown below.

It was demonstrated that esomeprazole magnesium 20 and 40 mg patients had a significant reduction in ulcer (≥ 5 mm) frequency compared to placebo (both p = 0.01).

Table 17: 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 magnesium 20 qd; E40 = esomeprazole magnesium 40 mg qd
*Log rank test p-value (vs. Placebo)

In Patients with Zollinger-Ellison Syndrome

Trial Design and Study Demographics
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 magnesium doses from 40 mg to 80 mg twice daily, with 1 patient receiving 80 mg t.i.d., for up to 12 months.

Study Results
For the trial duration, 14 of 21 patients were maintained and controlled on a esomeprazole magnesium dose of 40 mg b.i.d., and 5 patients were maintained and controlled on esomeprazole magnesium 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 magnesium per day. Esomeprazole was generally well tolerated in this patient population (see 8.2 Clinical Trial Adverse Reactions). Safety information does not extend beyond 1 year for esomeprazole magnesium doses 80 mg daily or higher, and was from a limited study population.

In Patients with *H. pylori*-Associated Active Duodenal Ulcer and a History of Duodenal Ulcer

Trial Design and Study Demographics
Studies were conducted in patients with *H. pylori*-associated active duodenal ulcers as well as with patients with a history of duodenal ulcers who were *H. pylori* positive.

Study Results
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 18: 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.

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 19: 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 + amoxicillin 1,000 mg + clarithromycin 500 mg, all twice daily for one week	89.7%	90.6%
Omeprazole 20 mg + amoxicillin 1,000 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 post-treatment, n = 400 (ITT analysis).

In Pediatrics (1-17 years of age)

Children (1- 11 years of age) with GERD

Trial Design and Study Demographics

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 magnesium 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 magnesium 5 mg or 10 mg
Weight ≥ 20 kg: once daily treatment with esomeprazole magnesium 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.

Study Results

The use of esomeprazole magnesium 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 magnesium for adults, and additionally from b) safety and a pharmacokinetic study performed in pediatric patients (see Pediatrics [1-17 years of age], 8.2.1

Clinical Trial Adverse Reactions – Pediatrics, Reflux Esophagitis - Study Results, and Nonerosive Reflux Disease [NERD] - Study Results).

Children (12-17 years of age) with GERD

Trial Design and Study Demographics

In a multicentre, randomized, 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 magnesium 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.

Study Results

The use of esomeprazole magnesium in pediatric patients (12-17 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 Pediatrics [12-17 years of age]); 8.2.1 Clinical Trial Adverse Reactions – Pediatrics, Reflux Esophagitis - Study Results; and Nonerosive Reflux Disease [NERD] Study Results).

14.3 Comparative Bioavailability Studies

Single-dose crossover comparative bioavailability study of Esomeprazole 40 mg Delayed-Release Capsules, was performed versus AstraZeneca Canada Inc.'s Nexium® (Delayed-Release Tablets), administered as 1 x 40 mg capsules/tablets in 30 healthy male and female volunteers / fast state. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Esomeprazole (1 x 40 mg capsule, Fast) From measured data Least Square Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	2,355.67 2,780.64 (50.7)	2,268.55 2,589.37 (55.9)	103.84	91.81 – 117.45
AUC_I (ng·h/mL)	2,563.23 2,888.54 (47.2)	2,304.57 2,647.74 (55.6)	111.22	105.52 – 117.24
C_{max} (ng/mL)	1,293.47 1,455.04 (40.7)	1,186.85 1,283.13 (43.9)	108.98	95.14 – 124.84
T_{max}§ (h)	1.75 (0.75-12.00)	1.75 (1.00-4.00)		
$T_{½}$€ (h)	1.16 (25.5)	1.19 (27.8)		

* pms-ESOMEPRAZOLE DR (esomeprazole magnesium) 40 mg delayed-release capsules (Pharmascience Inc.).

† Nexium® (esomeprazole magnesium) 40 mg delayed-release tablets (AstraZeneca Canada Inc.) were purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV %) only

Single-dose crossover comparative bioavailability study of Esomeprazole 40 mg Delayed-Release Capsules, was performed versus AstraZeneca Canada Inc.'s Nexium® (Delayed-Release Tablets), administered as 1 x 40 mg capsules/tablets in 110 healthy male and female volunteers / fed state. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Esomeprazole (1 x 40 mg capsule, Fed) From measured data Least Square Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	1,094.50 1,539.45(84.9)	1,166.92 1,736.51(100.1)	93.79	85.64 – 102.72
AUC_I (ng·h/mL)	1,197.81 1,622.41(83.3)	1,257.75 1,818.85 (97.6)	95.23	87.42 – 103.75
C_{max} (ng/mL)	415.64 569.24 (75.0)	407.99 544.92 (77.5)	101.87	90.64 – 114.49
T_{max}§ (h)	5.50 (2.00-9.00)	4.50 (1.50-7.50)		
$T_{½}$€ (h)	1.23 (48.3)	1.10 (50.5)		

* pms-ESOMEPRAZOLE DR (esomeprazole magnesium) 40 mg delayed-release capsules (Pharmascience Inc.).

† Nexium® (esomeprazole magnesium) 40 mg delayed-release tablets (AstraZeneca Canada Inc.) were purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

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 magnesium was studied in Wistar rats following oral and i.v. administration and compared to that of omeprazole. The effects of esomeprazole magnesium, 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 magnesium 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 hematological changes indicating a mild microcytic, hypochromic anemia (possibly due to an iron deficiency) were observed in adult rats, following repeat-dose oral treatment with high doses of esomeprazole magnesium or omeprazole. Similar slight changes were seen in pregnant rabbits, but no such changes were noted in esomeprazole magnesium -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.

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 tumor-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 tumor-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.

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.

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 tumors 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.

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 magnesium, 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.

Reproductive and Developmental Toxicology
Slight maternal toxicity was noted in pregnant rats treated orally with esomeprazole magnesium or omeprazole at doses of up to 280 mg/kg/day, but no adverse effects could be detected on embryo-fetal survival or development. The systemic exposure to esomeprazole magnesiumin 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 magnesium or omeprazole indicate any potential for disturbance of embryo-fetal development. However, severe and dose-related maternal toxicity was noted at relatively low doses and exposure of esomeprazole magnesium/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 magnesium was relatively low in many of the does, the highest dose level used could not be increased due to this maternal toxicity.

Juvenile Toxicity:
The plasma protein binding levels for esomeprazole magnesium 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 magnesium 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 magnesium 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 magnesium and omeprazole in juvenile rats and for esomeprazole magnesium 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 magnesium was given once daily or intermittently, once every 14 days. However, when the esomeprazole magnesium 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 magnesium 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 magnesium 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 magnesium 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 magnesium 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 magnesium in the dog liver microsomes, and it is therefore assumed that the metabolism of esomeprazole magnesium is mainly mediated by other CYP isoenzymes.

There was no unexpected toxicity and/or other effects following esomeprazole magnesium 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 magnesium dose levels in both neonatal/juvenile rats and dogs. This effect can be attributed to the high esomeprazole magnesium 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 anemia (which was probably due to an iron deficiency) was observed in both the esomeprazole magnesium-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 magnesium treatment, compared to adult animals.

17 SUPPORTING PRODUCT MONOGRAPHS

PrNEXIUM® (esomeprazole as esomeprazole magnesium trihydrate) delayed release tablets, 20 mg, 40 mg & delayed release granules, 10 mg, submission control number 251874, Product Monograph, AstraZeneca Canada Inc., Sept. 16, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-ESOMEPRAZOLE DR
Esomeprazole Magnesium Delayed-Release Capsules

Read this carefully before you start taking **pms-ESOMEPRAZOLE DR** 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 **pms-ESOMEPRAZOLE DR**.

What is pms-ESOMEPRAZOLE DR used for?
pms-ESOMEPRAZOLE DR 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 pipe).
- 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).

pms-ESOMEPRAZOLE DR is used in children 12-17 years old to treat:

- reflux esophagitis (tissue damage caused by the stomach acid and juices moving up the food pipe).
- 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 pms-ESOMEPRAZOLE DR work?
pms-ESOMEPRAZOLE DR is a medicine called a proton pump inhibitor (PPI).
pms-ESOMEPRAZOLE DR works by causing less acid to be made in your stomach.

What are the ingredients in pms-ESOMEPRAZOLE DR?
Medicinal ingredients: Esomeprazole magnesium dihydrate

Non-medicinal ingredients: Diacetylated Monoglycerides, Dimethicone Emulsion, Hydroxypropyl Methylcellulose, Mannitol, Methacrylic Acid-Ethyl Acrylate Copolymer (1:1) Dispersion 30%, Polysorbate 80, Stearyl Macrogolglycerides, Sugar Spheres, Talc, Triethyl citrate. The capsule shell is composed of Gelatin, Yellow Iron Oxide and Titanium Dioxide. The black ink is composed of Black Iron Oxide, Butyl Alcohol, Dehydrated Alcohol, Isopropyl Alcohol, Potassium Hydroxide, Propylene Glycol, Purified Water, Shellac, and Strong Ammonia.

pms-ESOMEPRAZOLE DR comes in the following dosage forms:
Delayed-Release Capsules: 20 mg and 40 mg esomeprazole (as esomeprazole magnesium dihydrate)

Do not use pms-ESOMEPRAZOLE DR if you:
- are allergic to esomeprazole, substituted benzimidazoles or any of the other ingredients of pms-ESOMEPRAZOLE DR or component of the container (see What are the ingredients in pms-ESOMEPRAZOLE DR?).
- are taking rilpivirine, a medicine used to treat HIV infection.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-ESOMEPRAZOLE DR. Talk about any health conditions or problems you may have, including if you:
- have had any health problems in the past.
- are breastfeeding or planning to breastfeed.
- are due to have a specific blood test (Chromogranin A).

Other warnings you should know about:
pms-ESOMEPRAZOLE DR is not recommended for use in patients under 12 years of age. This medicine should be used at the lowest dose and for the shortest time suitable for your condition. Talk to your healthcare professional if you have any concerns about your treatment.

Serious Side Effects: pms-ESOMEPRAZOLE DR can cause serious side effects, including:
- **Serious Skin Reactions:** In very rare cases, serious or life-threatening skin reactions have been reported with PPIs, such as esomeprazole magnesium.
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Stevens-Johnson Syndrome (SJS)
  - toxic epidermal necrosis (TEN)
  - erythema multiforme
  - acute generalized exanthematous pustulosis (AGEP)
- **Serious Stomach and Intestine Problems:** pms-ESOMEPRAZOLE DR can cause serious stomach and intestine problems. Tell your healthcare professional about 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.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Antibiotics: If you take antibiotics while taking pms-ESOMEPRAZOLE DR you may:
- experience symptoms such as severe (bloody or repeated watery) diarrhea, with or without fever, abdominal pain or tenderness. These are symptoms of bowel inflammation caused by a bacterial infection (*Clostridium difficile*).

If this happens, stop taking the drug combination and tell your healthcare professional immediately.

pms-ESOMEPRAZOLE DR should not be used in combination with the antibiotic clarithromycin during pregnancy or when breastfeeding, unless your healthcare professional tells you. Clarithromycin may harm your unborn baby or newborn.

Pregnancy: Tell your healthcare professional if you are pregnant or planning to become pregnant. There are specific risks you must discuss with your healthcare professional.

Long-term use of pms-ESOMEPRAZOLE DR:
Long-term use of pms-ESOMEPRAZOLE DR 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 healthcare professional about this risk.
- 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.
- increase risks of broken bones of the hip, wrist or spine. This is more likely to happen if you use pms-ESOMEPRAZOLE DR every day for a year or longer. Talk to your healthcare professional about this risk.
- cause a growth in your stomach (polyp) especially after one year.

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 pms-ESOMEPRAZOLE DR:
- Medications that prevent blood clots such as warfarin, acetylsalicylic acid and clopidogrel. Use of pms-ESOMEPRAZOLE DR with clopidogrel should be avoided as it may decrease the effectiveness of clopidogrel.
- Medicines used to treat HIV such as atazanavir, nelfinavir and saquinavir.

pms-ESOMEPRAZOLE DR may decrease the effectiveness or increase side effects of some medicines used to treat HIV. pms-ESOMEPRAZOLE DR should not be used with atazanavir, nelfinavir or saquinavir.
- Methotrexate, used in high doses to treat cancer. Your healthcare professional may tell you to stop taking pms-ESOMEPRAZOLE DR temporarily while you are taking methotrexate.
- Medicines used to treat fungal infections such as itraconazole, ketoconazole, and voriconazole
- Diazepam, used to treat anxiety
- Phenytoin, used to treat epilepsy
- Cisapride (not available in Canada), used to help empty the stomach
- Tacrolimus, used to lower the risk of organ rejection
- Cilostazol (not available in Canada), used to treat poor circulation in the legs
- Digoxin, used to treat heart disorders
- Medicines used to treat tuberculosis such as rifampin
- Herbal medicines such as St. John's Wort
- Medicines used in cancer therapy such as erlotinib

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

How to take pms-ESOMEPRAZOLE DR:
Follow your healthcare professional's directions carefully. They may be different from the information contained in this leaflet.
- Take all doses of pms-ESOMEPRAZOLE DR that your healthcare professional 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 pms-ESOMEPRAZOLE DR 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 *Helicobacter pylori* infection.
- Take pms-ESOMEPRAZOLE DR until your healthcare professional tells you to stop. Even if you start to feel better in a few days, your symptoms may return if pms-ESOMEPRAZOLE DR is stopped too soon. pms-ESOMEPRAZOLE DR needs to be taken for the full treatment duration to help correct acid problems.
- pms-ESOMEPRAZOLE DR may be taken with food or on an empty stomach.
- The capsule may be swallowed whole with water.
- The capsules may also be opened and the granules inside carefully emptied in half a glass of non-carbonated water. This will make it easier to swallow. Be sure to swallow all the tiny granules that come out of the capsule without chewing them. Don't let the granules 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 healthcare professional may tell you to take pms-ESOMEPRAZOLE DR:

- 20 to 40 mg once a day for 2 to 8 weeks.
- Continue taking pms-ESOMEPRAZOLE DR 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 (clarithromycin and amoxicillin).

Maintenance Treatment of NERD (on-demand) Dose

After first treatment of NERD, your healthcare professional may suggest that you take pms-ESOMEPRAZOLE DR 20 mg once daily, as needed, if symptoms of heartburn and regurgitation return once in a while.

Contact your healthcare professional if your symptoms get worse, won't go away, or if new symptoms arise.

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.

pms-ESOMEPRAZOLE DR is not recommended for use in children under 12 years of age.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-ESOMEPRAZOLE DR, contact a 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 pms-ESOMEPRAZOLE DR, and remember within 12 hours, take the capsule 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 pms-ESOMEPRAZOLE DR?

These are not all the possible side effects you may have when taking pms-ESOMEPRAZOLE DR. If you experience any side effects not listed here, tell your healthcare professional.

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

Common side effects include:

- Nausea
- Stomach upset
- Diarrhea
- Headache

Uncommon side effects include:

- Dry mouth
- Dizziness
- Insomnia
- Feeling of burning/prickliness/numbing
- Swelling of extremities
- Feeling sleepy
- Feeling like you or your surroundings are moving (vertigo) Rare side effects include:
- 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 healthcare professional's instructions when stopping pms-ESOMEPRAZOLE DR.

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			
Blood disorders (low white and/or red blood cell count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		✓	
Blurred vision		✓	
Confusion		✓	
Depression		✓	
Feeling ill		✓	
Gastrointestinal fungal infection: diarrhea, vomiting, melena, hemorrhage, abdominal pain, and fever		✓	

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**	
Hepatitis (inflammation of liver): skin and eyes appear yellow			✓
Myalgia (muscle pain): aching muscles, tenderness or weakness		✓	
Photosensitivity (sensitivity to sunlight): itchy, red skin when exposed to sunlight		✓	
Severe allergic reaction: shortness of breath, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, swelling or anaphylactic reaction/shock			✓
Shortness of breath		✓	
Skin reactions: rash, dermatitis, itching and/or hives		✓	
Sore joints		✓	
Stomatitis (mouth sores, redness and swelling of the lining of the mouth): inflammation in the mouth		✓	
VERY RARE			
Aggressive behaviour		✓	
***Clostridium difficile* colitis** (bowel inflammation): severe or persistent diarrhea, abdominal pain, nausea and vomiting, fever		✓	
Decreased consciousness		✓	
Gynecomastia: breast enlargement in men (and /or women)		✓	
Hallucinations: seeing or hearing things that are not there		✓	
Hypomagnesemia (low level of magnesium in the blood): abnormal eye movements, fatigue, muscle spasms or cramps, muscle weakness, numbness		✓	

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**	
Liver failure (serious disturbance of liver function, hepatic failure): yellow colour to skin, whites of the eyes (jaundice), bleeding easily, swollen abdomen, mental disorientation or confusion, sleepiness, coma		✓	
Muscular weakness		✓	
Nephritis (inflammation of the kidney): decreased appetite, difficulty breathing, fatigue, frequent urination, itchiness, nausea, vomiting		✓	
Serious skin reactions: • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish) • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough			✓
UNKNOWN			
Subacute cutaneous lupus erythematosus: new or worsening joint pain, rash on your cheeks or arms that gets worse in the sun			✓

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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 all capsules sealed in the blister strips until it is time for a dose. If you do not, moisture from the air may damage the drug.

Store pms-ESOMEPRAZOLE DR between 15°C and 25°C, in a dry place.

Do not keep pms-ESOMEPRAZOLE DR in the bathroom medicine cabinet or other warm, moist places. Do not use pms-ESOMEPRAZOLE DR after the expiry date marked on the pack.

Keep out of reach and sight of children.

If you want more information about pms-ESOMEPRAZOLE DR:
- 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: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug- product-database.html or by contacting the sponsor Pharmascience Inc. at: 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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