PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pmsc-ESOMEPRAZOLE DR

Esomeprazole Delayed Release Tablets

Delayed release tablets, 20 mg, 40 mg, Oral use

H^+, K^+-ATPase Inhibitor

PHARMASCIENCE INC
6111 Royalmount Ave., Suite 100
Montréal, Quebec
Canada H4P 2T4

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General	06-2022
7 WARNINGS AND PRECAUTIONS, Gastrointestinal	06-2022
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	06-2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pmsc-ESOMEPRAZOLE DR (esomeprazole magnesium) 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

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

1.1 Pediatrics

Pediatrics (12-17 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of esomeprazole in pediatric patients has been established. Therefore, Health Canada has authorized the following indication for pediatric use. pmsc-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

pmsc-ESOMEPRAZOLE DR (esomeprazole) **is contraindicated:**

- in patients who are hypersensitive to esomeprazole, 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
- with co-administration of rilprivirine 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

DO NOT administer via naso-gastric feeding tubes.

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 pmsc-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 pmsc-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 pmsc-ESOMEPRAZOLE DRonce 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 pmsc-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 pmsc-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 pmsc-ESOMEPRAZOLE DRonce 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.

Pediatrics (12-17 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).
- Safety studies in pediatric subjects do not extend beyond 8 weeks.

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

Nonerosive Reflux Disease (NERD): Doses over 1 mg/kg/day have not been studied. There are currently no data on appropriate doses for children with hepatic impairment (see 7.1.3 Pediatrics). In pediatric patients (12-17 years of age) with heartburn and/or acid regurgitation, without esophagitis, the recommended dose is 20 mg pmsc-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 pmsc-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

Tablets:
- The tablets should be swallowed whole with sufficient water.
- Do not disperse, divide, crush or chew the tablets.

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 (280 mg), demonstrated symptoms that were transient, and included weakness, loose stools and nausea. Single doses of 80 mg esomeprazole have

been shown to be uneventful. No specific antidote is known. Esomeprazole is extensively protein-bound and is therefore not readily dialyzable. Treatment should be symptomatic and general supportive measures should be utilized.

The maximum non-lethal oral dose in male and female rats ranged from 240 to 480 mg/kg (see 16 NON-CLINICAL TOXICOLOGY).

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 and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Delayed Release Tablet / 20 mg and 40 mg esomeprazole	Crospovidone, hypromellose, hydroxypropyl cellulose, glyceryl monostearate, macrogol, magnesium stearate, methacrylic acid ethyl acrylate copolymer, microcrystalline cellulose, polysorbate 80, povidone K30, sodium stearyl fumarate, sugar spheres, talc and triethyl citrate. The tablet film coating contains: Hypromellose, iron oxide red, iron oxide yellow, macrogol and titanium dioxide. The tablet imprinting contains: Iron oxide black, propylene glycol and shellac glaze.

Packaging and Description

pmsc-ESOMEPRAZOLE DR Tablets are formulated for oral administration and are available as 20 mg and 40 mg tablets with the following descriptions:

pmsc-ESOMEPRAZOLE DR 20 mg tablets are supplied as light pink tablets, elliptically shaped, biconvex, with A159 printed in black ink on one side.

pmsc-ESOMEPRAZOLE DR 40 mg tablets are supplied as pink tablets, elliptically shaped, biconvex, with A160 printed in black ink on one side.

pmsc-ESOMEPRAZOLE DR 20 mg tablets are available in HDPE bottles of 100 tablets, and in unit dose blister packs of 30 tablets (blister strip of 10 tablets).

pmsc-ESOMEPRAZOLE DR 40 mg tablets are available in HDPE bottles of 100 tablets, and in unit dose blister packs of 30 tablets (blister strip of 10 tablets).

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.

pmsc-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).

Antibiotic Combination Therapy:

Pseudomembranous Colitis:
Pseudomembranous Colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

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

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

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

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

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

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

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

  If the combination of pmsc-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 pmsc-ESOMEPRAZOLE DR should not

exceed an equivalent dose omeprazole of 20 mg daily (see atazanavir Product Monograph).

- Saquinavir **:** If pmsc-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 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 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 10, 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

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

Cyanocobalamin (Vitamin B_{12}) Deficiency:
The prolonged use of PPIs, may impair the absorption of protein-bound Vitamin B_{12} and may contribute to the development of cyanocobalamin (Vitamin B_{12}) deficiency.

Genetic Polymorphism:
The CYP 2C19 and CYP 3A4 isozymes are responsible for metabolism of esomeprazole.
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 pmsc-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 pmsc-ESOMEPRAZOLE DR is instituted as treatment with pmsc-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 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 is decreased in patients with severe liver dysfunction (Child Pugh Class C) resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. The plasma elimination half-life in patients with severe liver dysfunction is still very short (3 hours) relative to the dosing interval (24 hours). Esomeprazole and its major metabolites do not show any tendency to accumulate with once-daily dosing. Dose adjustment is not required in patients with mild to moderate liver impairment. A daily dose of 20 mg in patients with severe liver disease should not, as a rule, be exceeded (see 4.2 Recommended Dose and Dosage Adjustment).

Immune

Subacutecutaneous 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 pmsc-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, pmsc-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 does not support the need for routine laboratory monitoring of response to therapy. See Carcinogenesis and Mutagenesis for effects of esomeprazole 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 but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function. Esomeprazole is extensively protein-bound and is, therefore, not expected to be readily dialyzable. Dose adjustment is not required in patients with impaired renal function (see 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 in pregnancy has not been established. pmsc-ESOMEPRAZOLE DR should not be administered to pregnant women unless the expected benefits outweigh the potential risk s.

pmsc-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 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 Sisomer of omeprazole, which

is secreted in breast milk. Therefore, pmsc-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 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 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).

No data is currently available in children (1-11 years of age) with hepatic insufficiency (see 4 DOSAGE AND ADMINISTRATION).

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

7.1.4 Geriatrics

Geriatrics (> 71 years of age): The metabolism of esomeprazole is not significantly changed in elderly subjects. Following repeated oral dosing with 40 mg esomeprazole 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 is well-tolerated. Most adverse reactions have been mild and transient, showing no consistent relationship with treatment.

Adverse reactions have been recorded during controlled clinical investigations in >8500 adult patients exposed to esomeprazole. Additionally >1200 adult subjects/patients were exposed to esomeprazole 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.

Adverse reactions have also been recorded during a clinical investigation in 149 pediatric patients (12-17 years of age) exposed to esomeprazole. The treatment related adverse event profile was found to be consistent with that seen in adults.

8.2 Clinical Trial Adverse 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, irrespective of causal relationship, were reported in controlled short-term (up to 8 weeks) clinical trials involving 5668 patients:

Table 2 Adverse Reactions (>1%), Irrespective of Causal Relationship, in Short Term Clinical Trials (Up to 8 weeks) Treated With Esomeprazole.

Adverse Reaction	All studies	Placebo controlled studies	
	Esomeprazole (20 & 40 mg) n = 5668 (%)	Esomeprazole (20 & 40 mg) n = 470 (%)	Placebo n = 240 (%)
Gastrointestinal Disorders			
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 (10, 20 & 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 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 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%).

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 Reactions	Esomeprazole (20 & 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 by the investigator) were each reported at a frequency of >1% in clinical trials for the healing of gastric ulcers; gastric ulcer aggravated, mucosal discoloration GI, gastrointestinal symptoms NOS, esophageal stricture, esophagitis, vomiting, constipation, duodenitis, rash, anxiety, pharyngitis, respiratory infection, sinusitis, urinary tract infection, accident and/or injury, and back pain.

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

Risk-reduction of Gastric Ulcers Associated with NSAID Therapy

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

Table 5 Adverse Reactions 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 & 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 by the investigator) were each reported at a frequency of >1% in clinical trials for the risk-reduction of gastric ulcers; arthralgia, arthrosis, aggravated rheumatoid arthritis, cramps, myalgia, rash, urticaria, dizziness, headache, neuropathy, insomnia, constipation, duodenitis, epigastric pain, gastric mucosal lesion NOS, mucosal discoloration GI, esophageal disorder, esophagitis, vomiting, dry mouth, increased SGOT, increased SGPT, bronchitis, coughing, dyspnoea, pharyngitis, respiratory infection, sinusitis, anemia, thrombocythemia, micturation frequency, urinary tract infection, benign GI neoplasm, accident/or injury, back pain, chest pain, fatigue, peripheral edema, pain, and postoperative complications.

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

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 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) 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) 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 pmsc-ESOMEPRAZOLE DR 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, AstraZeneca's post-marketing safety database has received 48 medically confirmed case reports with 84 adverse events in children between 12 and 17 years of age. Five of the 48 cases were reported within approved label use, while 43 cases constituted off -label use. An overall assessment of the adverse events reported after within-label and off-label use in children ages 12-17 years raised no safety concerns with esomeprazole treatment in this age group.

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 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 serum levels by decreasing the rate of esomeprazole's metabolism. Drugs known to induce CYP 2C19 or CYP 3A4 or both (such as rifampin and St. John's Wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

With on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole, should be considered when pmsc-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 (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 (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 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/75mg daily maintenance dose) (metabolized by CYP2C19) and esomeprazole (40 mg once daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

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

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

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum leve ls of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA (see **General**).

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

Phenytoin: Concomitant administration of 40 mg esomeprazole (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 versus other drugs indicate that daily doses of 40 mg esomeprazole, 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 with a combined inhibitor of CYP 2C19 and CYP 3A4, such as voriconazole, may result in more than double the levels of esomeprazole exposure.

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

Digoxin: The absorption of digoxin can increase during treatment with esomeprazole and other drugs that reduce gastric acidity. Concomitant treatment with omeprazole (20 mg daily) and digoxin in ten healthy subjects increased the bioavailability of digoxin by an average of 10% (up to 30% in two out of ten subjects). Therefore, patients may need to be monitored when digoxin is taken concomitantly with pmsc-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 pmsc-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 pmsc-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 (1000/100 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 although this has no significant influence on the effect of esomeprazole 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, pmsc-ESOMEPRAZOLE DR 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

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

Esomeprazole magnesium (a substituted benzimidazole), reduces gastric acid secretion through a highly targeted mechanism of action. 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 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 40 mg vs. Esomeprazole 20 mg

Other Pharmacodynamic Effects

In some patients receiving esomeprazole, 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 of After Oral Administration for 5 days (% CV)

	C_{max} (µmol/L)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{(0-\infty)}$ (µmol*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 T_{max}, which is the arithmetic mean.

Absorption

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

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

Food intake delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole 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 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 pmsc-ESOMEPRAZOLE DR based on CYP 2C19 status is not necessary (see Endocrine and Metabolism, and Genetic Polymorphism).

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

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

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

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

Data presented are geometric means for AUC, C_{max} and $t_{1/2\ \lambda z}$ and median value for t_{max}
Duration of treatment for 12 - 17 year olds and adults were 8 days and 5 days, respectively.
Data were obtained from two independent studies.

- **Geriatrics:** The metabolism of esomeprazole is not significantly changed in elderly

subjects. Following repeated oral dosing with 40 mg esomeprazole 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 at controlled room temperature (15°C – 25°C).
Keep in a safe place out of reach and sight of children.
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

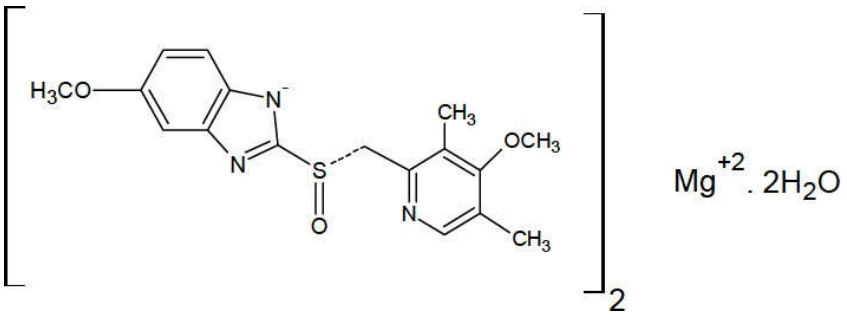
Proper name: Esomeprazole Magnesium Dihydrate

Chemical name: (T-4)-Bis [5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl) Methyl] sulfinyl] -1H-benzimidazolato] magnesium dihydrate

Molecular formula: $C_{34}H_{36}MgN_6O_6S_2$, $2H_2O$,

Molecular mass: 749.17 g/mol

Structural formula:



Physicochemical properties: White or slightly coloured powder, slightly hygroscopic.

Solubility: It is freely soluble in dimethylformamide and DMSO, soluble in methanol, and insoluble in methylene chloride and heptane.

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 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 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 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 (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 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 9 **Results of On-Demand Treatment Studies of Patients with Symptoms of GERD, Without Macroscopic Esophagitis. Proportion of Patients Unwilling to Continue On-Demand Therapy, ITT analysis**

	Esomeprazole 40	Esomeprazole 20	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 (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 (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 10 Observed Gastric Ulcer Healing Rates in Complete ITT Population Regardless of NSAID Type.

	Study 5			Study 6			Pooled		
	E40 n=129	**E20 n=138**	**R150 n=132**	**E40 n=133**	**E20 n=138**	**R150 n=139**	**E40 n=262**	**E20 n=276**	**R150 n=271**
Ulcer healing rate at 4	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
p-value[a]	<0.001[b]	0.003[b]	-	0.047	0.073	-	<0.001[b]	<0.001[b]	-

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

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

b statistically significant vs. R150 (Hochberg adjusted)

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

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

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

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

Risk-Reduction of Gastric Ulcers Associated with NSAID Therapy, Including COX-2 Selective NSAIDs

Trial Design and Study Demographics
In two large multicentre, randomized, double-blind placebo-controlled trials, esomeprazole (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 (20 mg or 40 mg) once daily was effective, safe and well-tolerated in combination with continuous NSAID use.

Patients treated with esomeprazole 40 mg or 20 mg had significantly higher estimated ulcer-free rates compared to placebo as shown below.

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

Table 12 **Proportion of Patients Without Gastric or Duodenal Ulcer by Month 6 in an ITT population.**

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

E20 = esomeprazole 20 qd; E40 = esomeprazole 40 mg qd

*Log rank test p-value (vs. Placebo)

In Pediatrics (12-17 years of age)

Children (12-17 years of age) with GERD

Trial Design and Study Demographics

In a multicentre, randomised, double-blind, parallel study (n=149; 89 female, 124 Caucasian, 15 Black, 10 Other) pediatric patients (12-17 years of age) with clinically diagnosed GERD were treated with either esomeprazole 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 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 for adults, and additionally from b) safety and pharmacokinetic studies performed in pediatric patients (see Pediatrics (12-17years 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

A randomized, double-blinded, two treatment, two period, two sequence, single dose crossover bioequivalence study of pmsc-ESOMEPRAZOLE DR (esomeprazole magnesium dihydrate) 40 mg delayed release tablets (Pharmascience Inc.) and NEXIUM® (esomeprazole magnesium trihydrate) 40 mg delayed release tablets (AstraZeneca Canada Inc.) was conducted in 42 in healthy adult male volunteers under fasting conditions. A summary of the bioavailability data from 38 subjects who completed the study is presented in the following table.

Table 13 Comparative Bioavailability Data for pmsc-ESOMEPRAZOLE DR Tablets vs Nexium® Delayed Release Tablets Administered under Fasting Conditions

Esomeprazole (1 x 40 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
AUC_T (mcg·h/mL)	7.14 7.94 (44.96)	7.47 8.35 (45.22)	95.62	89.53 - 102.12
AUC_I (mcg·h/mL)	7.27 8.07 (44.90)	7.61 8.51 (45.33)	95.47	89.45 - 101.90
C_{max} (mcg/mL)	2.06 2.16 (33.01)	2.30 2.42 (29.00)	89.78	84.45 - 95.44
T_{max}§ (h)	2.25 (1.50 - 4.50)	2.25 (1.25 – 4.00)		
$T_{½}$ ¶ (h)	1.82 (28.07)	1.81 (25.46)		

* pmsc-ESOMEPRAZOLE DR (esomeprazole magnesium dihydrate) 40 mg delayed release tablets (Pharmascience Inc.)

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

§ Expressed as median (range) only

¶ Expressed as arithmetic mean (CV%) only

A randomized, double-blinded, two treatment, two period, two sequence, single dose crossover bioequivalence study of pmsc-ESOMEPRAZOLE DR (esomeprazole magnesium dihydrate) 40 mg delayed release tablets (Pharmascience Inc.) and NEXIUM® (esomeprazole magnesium trihydrate) 40 mg delayed release tablets (AstraZeneca Canada Inc.) was conducted in 68 healthy adult male volunteers under fed conditions. A summary of the bioavailability data from 66 subjects who completed the study is presented in the following table.

Table 14 Comparative Bioavailability Data for pmsc-ESOMEPRAZOLE DR Tablets vs Nexium® Delayed Release Tablets Administered under Fed Conditions

Esomeprazole (1 x 40 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
AUC_T (ng·h/mL)	4516.83 5427.19 (54.09)	4153.62 5163.92 (56.34)	108.74	101.33 - 116.70
AUC_I (ng·h/mL)	4831.75 5767.37 (55.70)	4523.99 5673.41 (52.18)	106.80	99.94 - 114.14
C_{max} (ng/mL)	919.73 1052.30 (47.82)	955.40 1119.70 (48.15)	96.27	88.46 - 104.77
T_{max}§ (h)	5.25 (2.50 - 12.00)	5.00 (2.00 - 10.00)		
$T_{½}$¶ (h)	2.19 (41.46)	2.07 (31.98)		

* pmsc-ESOMEPRAZOLE DR (esomeprazole magnesium dihydrate) 40 mg delayed release tablets (Pharmascience Inc.)

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

§ Expressed as median (range) only

¶ Expressed as 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 15 Single-dose Toxicity Studies of Esomeprazole.

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

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

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

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

Repeat-dose Toxicity

The repeat-dose toxicity of esomeprazole was studied in rats (Wistar and Sprague-Dawley) and dogs after oral administration. Rats received oral doses of 14-280 mg/kg, and dogs 0.66-28 mg/kg, for up to 3 months. Esomeprazole has a low systemic toxicity. Some slight 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 or omeprazole. Similar slight changes were seen in pregnant rabbits, but no such changes were noted in esomeprazole-treated dogs. In both rats and dogs, histopathological changes in the stomach at the intermediate and high dose levels (rats: 69 and 280 mg/kg; dogs:

5.5 and 28 mg/kg) consisting of dose-dependent chief cell atrophy, mucosal hyperplasia, and/or focal necrosis of gastric glands, were accompanied by a dose-dependent increase in stomach weight and serum gastrin levels. These changes were expected and consistent with previous observations following treatment with high doses of omeprazole. These effects are the results of gastrin stimulation and/or inhibition of gastric acid secretion.

Carcinogenicity

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

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 tumours and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8-140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found, and the ECL-cell hyperplasia seen after 12 months recovered to normal during the next 12 months of no treatment.

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

Mutagenicity

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

Reproductive and Developmental Toxicology

Slight maternal toxicity was noted in pregnant rats treated orally with esomeprazole or omeprazole at doses of up to 280 mg/kg/day, but no adverse effects could be detected on embryo-fetal survival or development. The systemic exposure to esomeprazole in these animals was substantially higher than that seen in the clinical situation, indicating an adequate margin of safety.

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

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

In juvenile rats and dogs, the exposure to esomeprazole was generally comparable between males and females, although there was a slight tendency towards a higher exposure in female than in male rats at the highest dose level on Dose Day 28. The Cmax for esomeprazole was

observed between 10 and 60 minutes in juvenile rats and generally at 20 minutes for juvenile dogs. The exposure generally increased more than proportionally to the increase in dose in both juvenile rats and dogs.

The AUC for esomeprazole and omeprazole in juvenile rats and for esomeprazole in juvenile dogs decreased notably with the duration of treatment and/or the age of the animals, resulting in 10-fold lower AUC values after 1 month's once-daily treatment in rats or 2 to 3 months once-daily treatment in dogs, compared to Dose Day 1. The decrease in exposure in dogs was similar, regardless of whether esomeprazole was given once daily or intermittently, once every 14 days. However, when the esomeprazole dosage was increased from once to twice daily dosing from Dose Day 28, both the AUC and Cmax following the second daily dose were higher than the values following the first daily dose, on most sampling occasions. Thus, administration of the 2nd dose resulted in a more than dose-proportional increase in exposure, and also AUC values that were only 3 -fold lower on Dose Day 91 compared to Dose Day 1. Thus, increasing the dose from once to twice daily administration of esomeprazole from Dose Day 28 resulted in an exposure on Dose Day 91 that was about 5-fold higher than that attained following once daily administration throughout the study.

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

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

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

As in the adult rats and pregnant rabbits, a mild microcytic, hypochromic anemia (which was probably due to an iron deficiency) was observed in both the esomeprazole -treated juvenile

rats and dogs. This reaction was more pronounced in the young animals compared to that seen previously in adult animals, was shown to be dose- and time-related, and was fully reversible by the end of the dose-free recovery period.

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. NEXIUM (delayed release tablets, 20 mg and 40 mg), submission control 251874, Product Monograph, AstraZeneca Canada Inc. SEP 16, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pmsc-ESOMEPRAZOLE DR
Esomeprazole Delayed Release Tablets

Read this carefully before you start taking **pmsc-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 a bout your medical condition and treatment and ask if there is any new information about **pmsc-ESOMEPRAZOLE DR**.

What is pmsc-ESOMEPRAZOLE DR used for:
pmsc-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 tube)
- symptoms of reflux disease (e.g. heartburn, backup of stomach content 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
- ulcers caused by nonsteroidal anti-inflammatory drugs (drugs for pain and sore joints)

pmsc-ESOMEPRAZOLE DR is used in children 12-17 years old to treat:
- reflux esophagitis (tissue damage caused by the stomach acids and juices moving up the food tube)
- symptoms of reflux disease (e.g. heartburn, backup of stomach contents to the throat)
- the 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 pmsc-ESOMEPRAZOLE DR work?
pmsc-ESOMEPRAZOLE DR is a medicine called a proton pump inhibitor (PPI). pmsc-ESOMEPRAZOLE DR works by causing less acid to be made in your stomach.

What are the ingredients in pmsc-ESOMEPRAZOLE DR?
Medicinal ingredients: esomeprazole magnesium dihydrate

Non-medicinal ingredients: crospovidone, hypromellose, hydroxypropyl cellulose, glyceryl monostearate, macrogol, magnesium stearate, methacrylic acid – ethyl acrylate copolymer, microcrystalline cellulose, polysorbate 80, povidone K30, sodium stearyl fumarate, sugar spheres, talc and triethyl citrate. In addition, the tablet film coating contains: hypromellose, iron oxide red, iron oxide yellow, macrogol and titanium dioxide, The tablet imprinting contains: iron oxide black, propylene glycol and shellac glaze.

pmsc-ESOMEPRAZOLE DR comes in the following dosage forms:
Tablets (delayed release): 20 mg and 40 mg

Do not use pmsc-ESOMEPRAZOLE DR if you:

- you are allergic to esomeprazole, substituted benzimidazoles or any of the other ingredients of pmsc-ESOMEPRAZOLE DR (see What are the ingredients in pmsc-ESOMEPRAZOLE DR?).
- you 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 pmsc-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:
pmsc-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 doctor if you have any concerns about your treatment.

Serious Side Effects: pmsc-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 pmsc-ESOMEPRAZOLE DR.
  - o Drug reaction with eosinophilia and systemic symptoms (DRESS),
  - o Stevens-Johnson Syndrome (SJS),
  - o toxic epidermal necrosis (TEN)
  - o erythema multiforme
  - o acute generalized exanthematous pustulosis (AGEP)

- **Serious Stomach and Intestine Problems:** pmsc-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:
  - o trouble swallowing.
  - o unplanned weight loss.
  - o vomiting blood or food.
  - o 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: While taking pmsc-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 tell your healthcare professional immediately.

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 pmsc-ESOMEPRAZOLE DR: Long-term use of pmsc-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 pmsc-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 pmsc-ESOMEPRAZOLE DR:

- Medications that prevent blood clots such as warfarin, acetylsalicylic acid and clopidogrel. Use of pmsc-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. pmsc-ESOMEPRAZOLE DR may decrease the effectiveness or increase side effects of some medicines used to treat HIV.
  pmsc-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 pmsc-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 pmsc-ESOMEPRAZOLE DR for short periods of time than if you take it every day.

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

- Take all doses of pmsc-ESOMEPRAZOLE DR that your doctor prescribes even when you or your child feel well. In some cases, doses every day are needed to control pain and symptoms, to correct acid problems and to help damaged areas heal.

- Take pmsc-ESOMEPRAZOLE DR until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if pmsc-ESOMEPRAZOLE DR is stopped too soon. pmsc-ESOMEPRAZOLE DR needs to be taken for the full treatment duration to help correct acid problems.
- pmsc-ESOMEPRAZOLE DR may be taken with food or on an empty stomach.

Tablets (delayed release):
- The tablet may be swallowed whole with water.
- Do not disperse, divide, crush or chew the tablets.

Usual dose:

Adults
Your healthcare professional may tell you to take pmsc-ESOMEPRAZOLE DR:
- 20 to 40 mg once a day for 2 to 8 weeks
- Continue taking pmsc-ESOMEPRAZOLE DR 20 mg each day. This is to keep your symptoms from coming back.

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

Children (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.

Overdose:

If you think you, or a person you are caring for, have taken too much pmsc-ESOMEPRAZOLE DR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even i f there are no symptoms.

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

What are possible side effects from using pmsc-ESOMEPRAZOLE DR?
These are not all the possible side effects you may feel when taking pmsc-ESOMEPRAZOLE DR. If you experience any side effects not listed here, contact 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 doctor's instructions when stopping pmsc-ESOMEPRAZOLE DR therapy.

Serious side effects and what to do about them			
	Talk to your healthcare professional		
Symptom / effect	**Only if severe**	**In all cases**	**Stop taking drug and get immediate medical help**
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		✓	
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 of ten, 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		✓	
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, talk to 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.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 tablets 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 pmsc-ESOMEPRAZOLE DR at controlled room temperature (15°C – 25°C).
- Do not keep pmsc-ESOMEPRAZOLE DR in the bathroom medicine cabinet or other warm, moist places.
- Do not use pmsc-ESOMEPRAZOLE DR after the expiry date marked on the pack.
- Keep pmsc-ESOMEPRAZOLE DR well out of the reach and sight of children.

If you want more information about pmsc-ESOMEPRAZOLE DR:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs- health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.pharmascience.com; or by calling 1-888-550-6060;

This leaflet was prepared by:
Pharmascience Inc.
Montréal, Quebec
Canada H4P 2T4

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