PRODUCT MONOGRAPH

[Pr]Omeprazole Magnesium Delayed Release Tablets

20 mg omeprazole (as omeprazole magnesium)

H^+, K^+-ATPase Inhibitor

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^{Pr}Omeprazole Magnesium Delayed Release Tablets

20 mg omeprazole (as omeprazole magnesium)

THERAPEUTIC CLASSIFICATION
H^+, K^+-ATPase Inhibitor

NOTE: When used in combination with amoxicillin, clarithromycin or metronidazole, the Product Monographs for those agents must be consulted and followed.

ACTIONS AND CLINICAL PHARMACOLOGY
Omeprazole inhibits the gastric enzyme H^+, K^+-ATPase (the proton pump) which catalyzes the exchange of H^+ and K^+. Omeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose-dependent. Daily oral doses of omeprazole 20 mg and higher showed a consistent and effective acid control. Information from clinical trials in patients with duodenal ulcers in remission indicate that omeprazole magnesium 20 mg tablets demonstrate the same inhibition of stimulated acid secretion and similar effect on 24-hour intragastric pH as omeprazole 20 mg capsules. The mean decrease in peak acid output after pentagastrin stimulation was approximately 70%, after 5 days of dosing with omeprazole magnesium 20 mg tablet once daily.

The 20 mg tablet and the 20 mg capsule are not bioequivalent in terms of plasma omeprazole AUC, C_{max} and t_{max}. Omeprazole magnesium 20 mg tablets demonstrate, after repeated dosing, increased plasma omeprazole AUC (18%) and maximum concentration (41%) in comparison to omeprazole 20 mg given as capsules.

The omeprazole capsule (as a multiple unit formulation) is usually emptied gradually from the stomach into the intestine. In contrast to the capsule, the tablet (as a single unit formulation) will enter the intestine and dissolve as one unit. Consequently, the absorption and first pass metabolism of the tablet take place only during a very limited period. This may be one of the reasons for the difference observed in the pharmacokinetic variables of the two formulations.

Omeprazole magnesium tablets are absorbed rapidly. Food has no effect on the bioavailability of the tablet. Peak plasma levels occur on average within 2 hours.

Omeprazole magnesium 20 mg tablets and omeprazole 20 mg capsules have an equivalent effect on the inhibition of stimulated acid secretion and on 24-hour intragastric pH. These data support the conclusion that omeprazole magnesium 20 mg tablet and omeprazole capsule can be used

with equivalent efficacy in the treatment of conditions where a reduction of gastric acid secretion is required.

The antisecretory effect of omeprazole is directly proportional to the AUC; it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

Treatment with omeprazole alone has been shown to suppress, but not eradicate *Helicobacter pylori (H. pylori)*, a bacterium that is strongly associated with acid peptic disease. Approximately, 90 to 100% of patients with duodenal ulcers, and 80% of patients with gastric ulcer, are infected with *H. pylori*. Clinical evidence indicates a synergistic effect between omeprazole and certain antibiotics in achieving eradication of *H. pylori*. Eradication of *H. pylori* is associated with symptom relief, healing of mucosal lesions, decreased rate of duodenal ulcer recurrence and long-term remission of peptic ulcer disease, and reducing the need for prolonged anti-secretory therapy.

There is no statistically significant change in the bioavailability (AUC, C_{max}) of amoxicillin during concomitant treatment with omeprazole, in healthy volunteers.

There is an increase in the bioavailability (AUC) and half-life of omeprazole, and bioavailability (AUC) and C_{max} of clarithromycin, during concomitant administration, in healthy volunteers.

There is no statistically significant change in the bioavailability (AUC, C_{max}) of metronidazole during concomitant treatment with omeprazole, in healthy volunteers.

Omeprazole undergoes first-pass metabolism by the cytochrome P-450 system, mainly in the liver, through CYP 2C19 and CYP 3A4. The CYP 2C19 isozyme, which is involved in the metabolism of all available proton pump inhibitors, exhibits polymorphism. Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP 2C19 enzyme and are called poor metabolisers.

Following i.v. administration and oral administration (capsules) of omeprazole, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces.

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

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

INDICATIONS AND CLINICAL USE

Omeprazole Magnesium Delayed Release Tablets are indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

- duodenal ulcer;
- gastric ulcer;
- NSAID-associated gastric and duodenal ulcers;
- reflux esophagitis;
- symptomatic gastroesophageal reflux disease (GERD) *i.e.*, heartburn and regurgitation;
- dyspepsia*: a complex of symptoms which may be caused by any of the organic diseases listed above, or upon investigation no identifiable organic cause is found (*i.e.*, functional dyspepsia);
- Zollinger-Ellison syndrome (pathological hypersecretory condition);
- eradication of *Helicobacter pylori* (*H. pylori*).

Omeprazole Magnesium Delayed Release Tablets, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with peptic ulcer disease associated with *Helicobacter pylori* infection. The optimal timing for eradication therapy in patients whose ulcer is not clinically active (*i.e.*, asymptomatic) remains to be determined.

The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial preventive effects has not yet been settled.

In dyspeptic patients with an *H. pylori* infection, the concurrent gastritis can be healed with appropriate eradication therapy.

* A working definition of dyspepsia would include the presence of epigastric pain/discomfort, with or without heartburn and regurgitation which may be accompanied by nausea, vomiting, bloating, belching, flatulence, early satiety or post-prandial fullness. Symptoms may occur either during the day or throughout the night.

CONTRAINDICATIONS

Hypersensitivity to omeprazole, substituted benzimidazoles or any of the components of this medication (see PHARMACEUTICAL INFORMATION).

Co-administration with rilpivirine is contraindicated.

WARNINGS

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

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75mg daily maintenance dose) and omeprazole (80 mg once daily, i.e., four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Based on these data, concomitant use of omeprazole and clopidogrel should be avoided. See PRECAUTIONS, Drug Interactions.

Concomitant use of Proton Pump Inhibitors (PPIs) with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate (see PRECAUTIONS, Drug Interactions).

Drug Interactions with Antiretroviral Drugs

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

Rilpivirine:

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

Atazanavir and Nelfinavir:

Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the REYATAZ AND VIRACEPT Product Monographs).

If the combination of omeprazole magnesium 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 omeprazole magnesium should not exceed 20 mg daily (see REYATAZ Product Monograph).

Saquinavir:

If Omeprazole Magnesium Delayed Release Tablets is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities, including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation are recommended. Dose

reduction of saquinavir should be considered from the safety perspective for individual patients (see INVIRASE Product Monograph).

Immune

Subacute cutaneous lupus erythematosus:

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

Gastrointestinal

Long-term use of omeprazole magnesium is associated with an increased risk of fundic gland polyps especially beyond one year (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Most fundic gland polyps are asymptomatic. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Interference with Laboratory Tests

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, Omeprazole Magnesium Delayed Release Tablets treatment should be stopped 14 days before CgA measurements (see PRECAUTIONS, Drug Interactions).

Use in Pregnancy

The safety of omeprazole in pregnancy has not been established. Omeprazole Magnesium Delayed Release Tablets should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Mothers

Omeprazole is secreted in breast milk. Omeprazole Magnesium Delayed Release Tablets should not be given to nursing mothers unless its use is considered essential.

Use in Children

The safety and effectiveness of omeprazole magnesium tablets in children have not yet been established.

PRECAUTIONS

General

Antibiotic Combination Therapy

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

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

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

Clostridium Difficile Associated Diarrhea

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

Use in the Elderly

Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Geriatrics (>71 years of age): Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Patients with Hepatic Insufficiency

Patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). A dose of 20 mg omeprazole capsules given once daily to these patients for 4 weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Renal Insufficiency

The disposition of intact omeprazole is unchanged in patients with impaired renal function, and no dose adjustment is needed in these patients (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules) (see DOSAGE AND ADMINISTRATION).

Information on the bioavailability of omeprazole magnesium 20 mg tablet in elderly patients, in patients with hepatic insufficiency, and in patients with renal insufficiency, as well as information or drug interactions are not currently available.

Carcinogenesis

The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life-span during administration with 14 -140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months' high-dose treatment of mice (14 -140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 7 years did not cause any carcinoids.

The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se (see TOXICOLOGY). Similar observations have been made after administration of histamine H_2-receptor blockers and also in partially fundectomized rats.

Short-term treatment and long-term treatment with omeprazole capsules in a limited number of patients for up to 6 years have not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

Endocrine and Metabolism

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

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

Musculoskeletal and Connective Tissue

Bone Fracture: Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Drug Interactions

The gastric acid suppression during treatment with omeprazole and other proton pump inhibitors might decrease or increase the absorption of drugs with gastric pH dependent absorption. Thus, it can be predicted that the absorption of drugs such as ketoconazole, itraconazole, and erlotinib

can decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

Omeprazole is metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The pharmacokinetics of the following drugs, which are also metabolized through the cytochrome P-450 system, have been evaluated during concomitant use of omeprazole capsules in humans: aminopyrine, antipyrine, clopidogrel, diazepam, phenytoin, warfarin (or other vitamin K antagonists), cilostazol*, theophylline, voriconazole, digoxin, propranolol, metoprolol, lidocaine, quinidine, ethanol, piroxicam, diclofenac and naproxen.

*not marketed in Canada

Omeprazole inhibits CYP 2C19, the major omeprazole metabolizing enzyme, and is partially metabolized by CYP 3A4. Drugs known to inhibit CYP 2C19 or CYP 3A4 or both (such as clarythromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of omeprazole'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 omeprazole serum levels by increasing omeprazole's rate of metabolism.

Antiretroviral Drugs

Rilpivirine

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

Atazanavir

Co-administration of Omeprazole Magnesium Delayed Release Tablets with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C_{max} and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir (see REYATAZ Product Monograph).

Nelfinavir

Co-administration of Omeprazole Magnesium Delayed Release Tablets 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 VIRACEPT Product Monograph).

Saquinavir

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

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

Aminopyrine and Antipyrine

After 14 days' administration of 60 mg omeprazole once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days' administration of 30 mg once daily, no significant changes in clearance were noted.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg once daily, ie, four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

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 omeprazole, were given concomitantly.

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

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

Diazepam, Phenytoin, Warfarin (or other vitamin K antagonists) and Cilostazol*

As Omeprazole Magnesium Delayed Release Tablets is metabolized through cytochrome P-450 2C19, it can alter the metabolism and prolong elimination of diazepam, warfarin (R-warfarin), phenytoin and cilostazol*.

*not marketed in Canada

Diazepam

Following repeated dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54%. The corresponding decrease after omeprazole 20 mg was 26%.

Warfarin (or other vitamin K antagonists)

Concomitant administration of omeprazole 20 mg in healthy subjects had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen. In patients receiving warfarin or other vitamin K antagonists, monitoring of INR (International Normalised Ratio) is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.

Phenytoin

Following three weeks' treatment with omeprazole 20 mg once daily, the steady-state plasma levels of phenytoin in epileptic patients already receiving concomitant phenytoin treatment were not significantly affected. Urinary excretion of phenytoin and its main metabolite were also unchanged.

After single intravenous and oral doses of omeprazole capsules 40 mg in young, healthy volunteers, the clearance of phenytoin was decreased by 15-20%, and half-life was prolonged by 20-30%. Following repeated dosing with omeprazole 40 mg once daily, the elimination half-life of phenytoin was increased by 27%. Thus, there appears to be a dose-dependent inhibition of elimination of phenytoin by omeprazole.

Patients receiving phenytoin and warfarin (or other vitamin K antagonists) should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Results from a range of interaction studies with omeprazole magnesium versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on other clinically relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP 1A2 (caffeine, phenacetin, theophylline), CYP 2C9 (S-warfarin), CYP 2D6 (metoprolol, propranolol), CYP 2E1 (ethanol), and CYP 3A (cyclosporin, lidocaine, quinidine, estradiol).

*Cilostazol**

Omeprazole, given in doses of 40 mg to health subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites, 3,4-dihydrocilostazol, by 29% and 69% respectively.

*not marketed in Canada

Methotrexate

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

Tacrolimus

Although no clinical studies have been undertaken, there is a possibility that the concomitant administration of omeprazole and tacrolimus may increase serum levels of tacrolimus.

Theophylline

No effects on oral or i.v. theophylline kinetics have been observed after repeated once-daily doses of 40 mg omeprazole.

Voriconazole

Concomitant administration of omeprazole and a CYP 2C19 and CYP 3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. However, a dose adjustment of omeprazole is not required.

Digoxin

The absorption of digoxin can increase during treatment with omeprazole 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).

Propranolol and Metoprolol

No effects on propranolol kinetics were observed in a steady-state trial with 20 mg of omeprazole daily. Similarly, no effects on steady-state plasma levels of metoprolol were observed after concomitant treatment with 40 mg omeprazole daily.

Lidocaine

No interaction with a single intravenous dose of lidocaine or its active metabolite, MEGX, was found after one week's pre-treatment with omeprazole 40 mg once daily. There were no interactions between omeprazole and lidocaine or MEGX concerning pharmacokinetic variables.

Quinidine

After one week of omeprazole 40 mg once daily, no effect was observed on the kinetics or pharmacodynamics of quinidine.

Ethanol

There was no significant effect on the pharmacokinetics of ethanol after omeprazole 20 mg.

Piroxicam, Diclofenac and Naproxen

There was no significant effect on the steady-state pharmacokinetics of piroxicam, diclofenac, and naproxen following repeated dosing with omeprazole 20 mg, in healthy volunteers.

Antacids

No interaction with antacids administered concomitantly with omeprazole (given as capsules) has been found.

Food

No interaction with food after repeated dosing of omeprazole magnesium tablets has been found.

Drug-Laboratory Interactions

During treatment with antisecretory drugs, CgA increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid

this interference, omeprazole magnesium treatment should be stopped 14 days before CgA measurements (see ACTIONS AND CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Omeprazole is well tolerated. Most adverse reactions have been mild and transient, and have shown no consistent relationship with treatment. Adverse events have been recorded during controlled clinical investigations in 2764 patients exposed to omeprazole (data taken from controlled clinical studies with omeprazole capsules) or reported from routine use. In a controlled clinical trial comparing omeprazole to placebo, the prevalence of adverse events with omeprazole 40 mg once daily was similar to that with placebo. In short-term comparative double-blind studies with histamine H_2-receptor antagonists, there was no significant difference in the prevalence of adverse events between omeprazole capsules and the H_2-receptor antagonists. An extensive evaluation of laboratory variables has not revealed any significant changes during omeprazole treatment which are considered to be clinically important.

The following adverse events (at a rate of more than 1%) have been reported in individuals receiving omeprazole capsules in controlled clinical situations: diarrhea (2.8%); headache (2.6%); flatulence (2.3%); abdominal pain (1.7%); constipation (1.3%); and dizziness/vertigo (1.1%).

The following is a list of adverse events reported in clinical trials or reported from routine use. Events are classified within body system categories. The following definitions of frequencies are used: common: ≥ 1/100; uncommon: ≥ 1/1000 and <1/100; rare: <1/1000, and very rare: <1/10000.

Central and Peripheral Nervous System: Common: headache. Uncommon: dizziness, paresthesia, somnolence, insomnia and vertigo. Rare: reversible mental confusion, agitation, aggression, depression and hallucination occurring predominantly in severely ill patients.

Endocrine: Rare: gynaecomastia.

Gastrointestinal: Common: diarrhea, constipation, abdominal pain, nausea/vomiting and flatulence. Rare: dry mouth, stomatitis, gastrointestinal candidiasis and microscopic colitis.

Hematological: Rare: leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.

Hepatic: Uncommon: increased liver enzyme levels. Rare: encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice and hepatic failure.

Musculoskeletal: Rare: arthralgia, muscular weakness and myalgia.

Skin: Uncommon: rash, dermatitis and/or pruritus, and uticaria. Rare: photosensitivity, erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis (TEN) and alopecia.

Other Adverse Events: Uncommon: malaise, hypersensitive reactions including urticaria Rare: hypersensitive reactions including angioedema, fever, bronchospasm and interstitial nephritis and anaphylactic shock; increased sweating, peripheral edema, blurred vision, taste disturbances and hyponatraemia. Very rare: hypomagnesaemia (severe hypomagnesaemia may result in hypocalcaemia, and hypomagnesaemia may also result in hypokalaemia).

***H. pylori* Eradication Combination Therapy:** The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 493 patients receiving omeprazole, amoxicillin and clarithromycin: diarrhea (28%), taste disturbances (15%), headache (5%), flatulence (4%), nausea (3%), abdominal pain (2%), ALT increased (1%), epigastric pain (1%), pharyngitis (1%) and glossitis (1%).

The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 494 patients receiving omeprazole, metronidazole and clarithromycin: taste disturbances (14%), diarrhea (13%), headache (6%), ALT increased (6%), flatulence (5%), nausea (5%), AST increased (5%), dyspepsia (3%), dry mouth (2%), dizziness/vertigo (2%), epigastric pain (1%), pharyngitis (1%), eructation (1%) and fatigue (1%).

Clinical experience with the use of omeprazole magnesium 20 mg tablet is limited. In two short term studies (20 mg tablet once daily for a maximum duration of 7 days) in a limited number of patients with duodenal ulcer in remission, the adverse event profile seen with the omeprazole magnesium 20 mg tablet is similar to that seen with the omeprazole 20 mg capsule.

Post-Market Adverse Drug Reactions

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

Musculoskeletal and Connective Tissue: Osteoporosis and osteoporosis-related fractures have been reported with multiple daily doses and long-term PPI therapy.

There have been post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (see WARNINGS, Immune).

There have been post-marketing reports of fundic gland polyps (PGPs) (See WARNINGS, Gastrointestinal).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. Single oral doses of up to 400 mg of omeprazole capsules have not resulted in any severe symptoms, and no specific treatment has been needed. One case report described that a single oral dose (560 mg) of omeprazole was associated with moderate increase of white blood cells, generalised malaise, nausea, vomiting, apathy, confusion, drowsiness, moderate headache, flatulence and abdominal pain. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored.

The oral LD_{50} of omeprazole in male and female rats and mice was greater than 4000 mg/kg. In dogs, the only sign of acute toxicity was vomiting, which occurred at doses of approximately 600 mg/kg (see TOXICOLOGY).

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

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

DOSAGE AND ADMINISTRATION

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

Duodenal Ulcer

Acute Therapy: The recommended adult oral dose is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, the recommended adult doses are 20 mg-40 mg given once daily. Healing is usually achieved within 4 weeks in such patients.

Gastric Ulcer

Acute Therapy: The recommended adult dose is 20 mg given once daily. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: In patients with gastric ulcer refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Gastric Ulcer: About 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended Omeprazole Magnesium Delayed Release Tablets dose is 20 mg once daily, increased to 40 mg once daily as necessary.

Reflux Esophagitis
Acute Therapy: The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks.

Symptomatic Gastroesophageal Reflux Disease (*i.e.*, Heartburn and Regurgitation)

The recommended adult dose is 20 mg given once daily. Symptom relief should be rapid. If symptom control is not achieved after 4 weeks, further investigation is recommended. **NSAID-Associated Gastric or Duodenal Ulcers**

The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial preventive effects has not yet been settled.

Acute Therapy: In patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily. Symptom resolution is rapid and healing usually occurs within 4 weeks. For those patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Maintenance Therapy: For the prevention of relapse in patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily, for up to 6 months.

Dyspepsia
Prior to treating patients presenting with dyspeptic symptoms, it should be determined that these symptoms are originating from the upper gastrointestinal tract. Patients presenting with alarm symptoms (see WARNINGS), and older patients who are at a greater risk of having a serious organic disease, should be investigated prior to the initiation of therapy. If the dyspeptic

symptoms are known to be related to a diagnosis of organic disease, the appropriate treatment regimen listed in the sections above should be employed.

If the dyspeptic symptoms are not known to be related to an organic disease, the recommended daily dose of Omeprazole Magnesium Delayed Release Tablets is 20 mg once daily for 4 weeks. If after 2 weeks' treatment the patient does not respond to therapy, or there is an early clinical indication of a lack of efficacy, the patient should be thoroughly investigated in order to rule out organic disease (see WARNINGS). If there are indications of a clinical response following the initial 2 weeks of treatment, Omeprazole Magnesium Delayed Release Tablets may be continued for an additional 2 weeks.

Epigastric pain/discomfort (with or without heartburn and regurgitation) as predominant symptoms, are likely to respond to acid suppression therapy. In all cases, patients who do not respond to 4 weeks' treatment, or whose symptoms recur shortly after discontinuation of treatment, with Omeprazole Magnesium Delayed Release Tablets should be investigated for underlying organic diseases.

***Helicobacter pylori* Associated Peptic Ulcer Disease**

Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is Omeprazole Magnesium Delayed Release Tablets 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days.

Omeprazole,Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is Omeprazole Magnesium Delayed Release Tablets 20 mg, metronidazole 500 mg and clarithromycin 250 mg, all twice daily for seven days.

To ensure healing and/or symptom control, further treatment with 20 mg Omeprazole Magnesium Delayed Release Tablets once daily for up to three weeks is recommended for patients with active duodenal ulcer, and with 20-40 mg Omeprazole Magnesium Delayed Release Tablets once daily for up to twelve weeks for patients with active gastric ulcer.

Patient compliance with treatment regimens for the eradication of *H. pylori* has been demonstrated to have a positive effect on eradication outcome. In clinical trials, patients treated with triple therapy regimens have shown high compliance rates.

Patients who fail to have their infection eradicated may be considered to have *H. pylori* resistant to the antimicrobials used in the eradication regimen. Therefore, therapy involving alternative effective antimicrobial agents should be considered (if re-treating).

In dyspeptic patients with an *H. pylori* infection, the concurrent gastritis can be healed with appropriate eradication therapy.

Zollinger-Ellison Syndrome

The dose used in the treatment of Zollinger-Ellison syndrome will vary with the individual patient.

The recommended initial dose is 60 mg, given once daily. More than 90% of patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20-120 mg omeprazole capsules daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg omeprazole capsules three times daily have been administered.

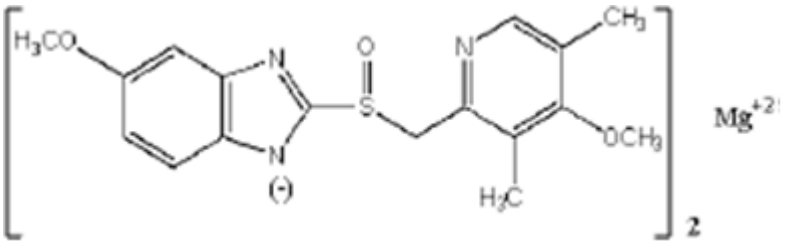
Patients with Renal Insufficiency: No dose adjustment is required (see PRECAUTIONS).

Patients with Hepatic Insufficiency: No dose adjustment is required. The daily dose should not exceed 20 mg (see PRECAUTIONS).

Elderly Patients: No dose adjustment is required. The daily dose should not exceed 20 mg (see PRECAUTIONS).

The tablets should be swallowed whole with sufficient water. The tablets must not be chewed or crushed.

PHARMACEUTICAL INFORMATION

(a) Drug Substance	
Proper name	omeprazole magnesium
Chemical Name	Di (5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl}-1H-benzimidazole) magnesium
Structural Formula	
Molecular Formula	$C_{34}H_{36}N_6O_6S_2Mg$
Molecular Weight	713.1 g/mol (anhydrous basis)
Description	Omeprazole magnesium is a off-white to light brown colored powder. It is sparingly soluble in methanol, freely soluble in N,N-Dimethyl formamide. The pKa of the benzimidazole (omeprazole base) is 8.8, and that of the pyridinium ion, 4.0.

Composition

Active:	mg/tablet
omeprazole magnesium amorphous	20.6 (corresponds to 20 mg omeprazole/tablet)

Nonmedicinal:
Hypromellose, iron oxide black and iron oxide red, lecithin, mannitol, meglumine, methacrylic acid copolymer dispersion, polyethylene glycol, simethicone emulsion, shellac glaze, sodium hydroxide, sodium starch glycolate, sodium stearyl fumarate, talc and titanium dioxide.

Stability and Storage Recommendations
Store in a dry place at 15°C to 30°C (59°F to 86°F). Protect from light.

AVAILABILITY OF DOSAGE FORMS

Omeprazole magnesium 20 mg delayed release tablets are dark pink colored, round biconvex, beveled edge enteric coated tablet with 'O20' imprinted with black ink on one side.

The 20 mg tablets are provided in bottles of 30's, 100's, and 500's.

PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Omeprazole differs from existing inhibitors of gastric acid secretion such as histamine H_2-receptor antagonists and anticholinergic agents in its ability to directly inhibit the gastric H^+, K^+-ATPase. This enzyme has been identified as the proton pump of the parietal cell.

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

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

Due to the potency and long duration of action of omeprazole, repeated administrations of high doses in the rat resulted in a marked decrease of acid secretion and a secondary hypergastrinemia and hyperplasia of G-cells. In rats, administration of omeprazole 14-140 mg/kg/day resulted in plasma gastrin levels of 1000-3000 pg/mL as compared to 150-200 pg/mL in controls. In dogs, high doses of omeprazole (28 mg/kg/day) produced marked hypergastrinemia (1000-2000 pg/mL after food intake), as compared to 100-300 pg/mL in controls. However, no hyperplasia of G-cells was evident in this species.

Secondary Pharmacological Effects

Mean arterial blood pressure and heart rate in the anesthetized dog were not affected by omeprazole under various challenges. Circulatory and respiratory functions in the dog were not affected by omeprazole, either at rest or during exercise. Omeprazole had no anticholinergic and no antihistamine (H_2-receptor) activity. In the rat, no effect on basal locomotor activity nor on exploratory activity was recorded, suggesting that omeprazole is devoid of sedative or neuroleptic effects.

Other Interactions

Omeprazole interacts with cytochrome P-450 in the rat liver. Omeprazole prolonged hexobarbital sleeping time by 12%.

Pharmacokinetics

Absorption and Distribution

Omeprazole is degraded rapidly in acidic gastric juice (rat and dog studies). Absorption is rapid. Peak plasma levels were found within 20 minutes and 1 hour after intra-duodenal and oral administration, respectively, in the dog. The drug has a low oral bioavailability, 5% in unstarved rats and 15-20% in starved male and female rats, if the drug is not protected by an enteric coating. The intra-duodenal bioavailability is approximately 70% and the oral bioavailability is approximately 15% in the dog. After absorption, omeprazole is rapidly distributed to extravascular sites, and about 95% is bound to plasma proteins. The distribution of ^{14}C-labelled omeprazole in the mouse was investigated by autoradiography. Radioactivity was initially found in the blood and most organs. Sixteen hours after administration, the drug was confined predominantly to the stomach wall. At 48 hours, the radioactivity was eliminated.

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

Metabolism and Excretion

Omeprazole was extensively metabolized in all species studied. In rats and dogs approximately 20-30% of the dose was excreted as urinary metabolites and the remainder by biliary excretion as metabolites in the feces. Elimination was virtually complete within 72 hours. Identifiable metabolites constituted about 50% (rat) and 70% (dog) of the total metabolite excretion in 24 hours, and about 12% of the given dose in both species.

A study in lactating rats showed that omeprazole is excreted in breast milk. The concentration in the milk at 3-5 hours post dose was 100-200 times lower than the plasma concentration. It is not known if omeprazole is excreted in human milk.

Human Pharmacology

Pharmacodynamics

In both normal volunteers and hypersecretors, omeprazole inhibited basal nocturnal and daytime acid secretion as well as meal-, histamine-, and pentagastrin-stimulated secretion (omeprazole capsule data).

Table 1 Percentate Inhibition of Mean Acid Output After Single Oral Doses of Omeprazole

(b) STIMULUS	(c) TYPE OF SUBJECT	(d) OMEPRAZOLE DOSE (mg)		(e) TIME AFTER DOSE (f) (h)
		(g) 20	(h) 80	
Basal	HSu*	33%		1-4
Basal-Nocturnal	DU(rem)***	49%		15-24
Sham Feeding	HSu	23%		1.5-3.5
Betazol	HSu	38%		1-4
Pentagastrin	HSu	36%		1-4
Basal	ZES***		97%	2-3

* healthy subject ** duodenal ulcer in remission ***Zollinger-Ellison syndrome

Repeated dosing with omeprazole capsule 20 mg once daily provided rapid inhibition of gastric acid secretion, with the maximum effect achieved within the first 4 days of treatment.

Information from clinical trials in patients with duodenal ulcers in remission indicates that omeprazole magnesium 20 mg tablets demonstrate the same inhibition of stimulated acid secretion and similar effect on 24-hour intragastric pH as omeprazole 20 mg capsules (mean proportion of time with pH >3 for capsule: 50.7%; for tablet: 57.35%). The mean decrease in peak acid output after pentagastrin stimulation was approximately 70%, after 5 days of dosing with omeprazole magnesium 20 mg tablet once daily.

Other Pharmacodynamic Effects

The effect of omeprazole on various organ systems has been investigated (data taken from clinical studies using omeprazole capsules). **No clinically significant effects** attributable to the drug could be found for the following parameters: *Endocrine:* plasma levels of insulin, C-peptide, glucagon, PTH, thyroid hormones or sex hormones, basal levels of cortisol; *Cardiovascular:* blood pressure, heart rate, electrocardiogram; *Renal:* renal handling of acid and electrolytes; *Hepatic:* liver enzymes. However, in some patients receiving omeprazole, elevated concentrations of alkaline phosphatase, S-AST and S-ALT have been reported (see ADVERSE REACTIONS).

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

No clinically significant CNS effects have been recorded.

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

Omeprazole has no effect on acetylcholine or H_2-receptors.

Pharmacokinetics

Omeprazole magnesium tablets are absorbed rapidly. Peak plasma levels occur on average within 2 hours. The 20 mg tablet and the 20 mg capsule are not bioequivalent in terms of plasma omeprazole AUC (geometric ratio and 90% confidence interval: 1.18, 1.06-1.30), C_{max} (1.41, 1.24-1.60) and T_{max}. Omeprazole magnesium 20 mg tablets demonstrate, after repeated dosing, increased plasma omeprazole AUC (18%) and maximum concentration (41%) in comparison to omeprazole 20 mg given as capsules.

Ninety-five to 100% of duodenal ulcer and 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy. Eradication of *H. pylori* is associated with long-term remission of peptic ulcer disease. Long-term treatment of these patients with anti-secretory agents is generally not recommended. Long-term treatment with omeprazole is effective in the prevention of relapse of duodenal or gastric ulcer, as demonstrated in clinical studies in patients with unknown *H. pylori* status, and may be used for the minority of patients who are *H. pylori*-negative.

The bioavailability of amoxicillin was studied during concomitant administration with omeprazole in fasting healthy adult subjects. When a single dose of amoxicillin, 750 mg, was administered to subjects who had received repeated doses of omeprazole 40 mg twice daily for 3 weeks, no significant change in the bioavailability (AUC, C_{max}) of amoxicillin was observed.

Clarithromycin 500 mg three times daily and omeprazole 40 mg capsules once daily were studied following concomitant administration in fasting healthy adult subjects. When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole t½ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, C_{min} and AUC_{0-8} of clarithromycin were increased by 10%, 27% and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

The omeprazole capsule (as a multiple unit formulation) is usually emptied gradually from the stomach into the intestine. In contrast to the capsule, the tablet (as a single unit formulation) will enter the intestine and dissolve as one unit. Consequently, the absorption and first pass metabolism of the tablet take place during a very limited period. This may be one of the reasons for the difference observed in the pharmacokinetic variables of the two formulations.

The antisecretory effect of omeprazole is directly proportional to the AUC, and thus it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

Omeprazole undergoes first-pass metabolism, and is completely metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The major part of its metabolism is dependent upon the polymorphically expressed, specific isoform, CYP 2C19 (S-mephenytoin hydroxylase). The remaining part is dependant on another specific isoform, CYP 3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP 2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP 2C19. However, due to low affinity to CYP 3A4, omeprazole has no potential to inhibit the metabolism of other CYP 3A4 substrates.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP 2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP 2C19 enzyme by omeprazole and/or its metabolites (eg. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Poor metabolisers: Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP 2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is expected to be catalysed by CYP 3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP 2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. However, these findings have no implication on dosing of omeprazole magnesium.

Following i.v. administration and oral administration (capsules) of omeprazole, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces. Less than 0.1% of the dose administered is excreted in urine as unchanged drug.

Six urinary metabolites have been detected. The two main metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. Three metabolites have been identified in plasma: the sulphide and sulphone derivatives and hydroxyomeprazole. It is unlikely that these metabolites contribute to inhibition of acid secretion.

Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). The mean urinary excretion of metabolites was 68% of the dose. These changes are consistent with reduction in presystemic and systemic elimination, typical in the elderly. The daily dose should, as a rule, not exceed 20 mg in this patient group (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The pharmacokinetics of omeprazole in patients with impaired renal function was virtually the same as in healthy subjects (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). However, patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). A dose of 20 mg given once daily to these patients for 4 weeks was well tolerated. Dosage for patients with liver cirrhosis and other liver dysfunction should, as a rule, not exceed 20 mg daily (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Information on the bioavailability of omeprazole magnesium 20 mg tablet in elderly patients, in patients with hepatic insufficiency, and in patients with renal insufficiency is not currently available.

Clinical Data

H. Pylori Eradication

Table 2 Results of Studies in Patients With a History of Duodenal Ulcer Who Were *H.Pylori* Positive.

(i)	(j) Treatment	(k) Eradication Rate	
		(l) APT or ITT Analysis	(m) PP Analysis
Study 1	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	96%	98%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	95%	94%
Study 2	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	94%	95%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	87%	91%

*500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety.
Study 1: Patients included in the APT and PP analyses were assessed for *H. pylori* status by UBT pre- and post treatment, n = 684 (APT analysis).
Study 2: Patients included in the ITT and PP analyses were assessed for *H. pylori* status by UBT and culture pre- and post-treatment, n = 514 (ITT analysis).

Table 3 Results Of Studies In Patients With Active Peptic Ulcer Who Were *H. Pylori* Positive (ITT Analysis).

(n)	(o) Treatment	Eradication Rate (PP analysis)	Ulcer Healing Rate (post - treatment)	(p) Rate of Patients in Remission (6 months after cessation of therapy)
Study 3	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	78% (87%)	92%	88%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	85% (92%)	94%	92%
Study 4	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	79% (83%)	94%	83%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	86% (93%)	96%	92%

*500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety.
Study 3: Patients with duodenal ulcer, included in the ITT analysis, were assessed for H. pylori status by UBT and histology pre- and post-treatment, n = 146 (ITT analysis).
Study 4: Patients with gastric ulcer, included in the ITT analysis, were assessed for H. pylori status by UBT and histology pre- and post-treatment, n = 145 (ITT analysis).

It has been demonstrated that resistance to metronidazole is a negative predictive factor, decreasing the eradication rate of *H. pylori* obtained with triple therapy (omeprazole, metronidazole and clarithromycin) by 10-20%. The addition of omeprazole to metronidazole and clarithromycin appears to reduce the effect of primary resistance and the development of secondary resistance compared to antimicrobials alone.

Susceptibility testing (MIC values derived from the Agar dilution method) of *H. pylori* to metronidazole and clarithromycin is available for 486 primary isolates from patients with a history of duodenal ulcer in one European study. Resistance to metronidazole (MIC >8 mg/L) was detected in 131 strains (27%), while 9 strains (2%) were resistant to clarithromycin (MIC >1 mg/L). Secondary resistance to metronidazole developed in strains from 4 patients treated with

omeprazole/metronidazole/clarithromyin. Similarly, in those patients treated with omeprazole/metronidazole/clarithromycin or omeprazole/amoxicillin/clarithromycin combinations, secondary resistance to clarithromycin developed in strains from 4 patients. For amoxicillin, the MIC values at pre-therapy or post-therapy did not indicate any primary, or the development of secondary, resistance to *H. pylori*.

Dyspepsia

The use of omeprazole in the management of dyspepsia has been examined in four randomized, double-blind, placebo-controlled and/or comparator trials. Following two or four weeks' therapy, omeprazole 20 mg daily provided complete relief of symptoms to significantly more patients than H_2-receptor antagonists or placebo. Gains in clinical benefit of 10-20% were reported. In open studies, daily doses of omeprazole 10 mg provided significant gains in clinical benefit over calcium carbonate/magnesium hydroxide antacid (10 mL q.i.d.) following four weeks of treatment. An escalating treatment regimen (escalation every 2 weeks, as needed, total of 16 weeks of treatment) consisting of 10, 20 and 40 mg omeprazole daily provided significant gains in clinical benefit over a treatment regimen consisting of calcium carbonate/magnesium hydroxide antacid and a H_2-receptor antagonist (antacid/alginate 10 mL q.i.d., escalating to the H_2-receptor antagonist 150 mg b.i.d. and then 150 mg q.i.d.).

Comparative Bioavailability Studies

A blinded, randomized, single oral dose, two way crossover comparative bioavailability study of Omeprazole Magnesium Delayed Release Tablets, 20 mg (Dr. Reddy's Laboratories Inc.) and PrLOSEC® (omeprazole magnesium) delayed release tablets 20 mg (AstraZeneca Canada Inc.) was conducted in 56 healthy, adult, male volunteers under fasting conditions. The results are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Omeprazole (1 x 20 mg) From measured dataGeometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.hr/mL)	1621.0663 2695.597 (100.33)	1657.7009 2676.949 (97.17)	97.8	(93.7, 102.1)
AUC_I (ng.hr/mL)	1660.1924 2748.362 (100.45)	1719.5885 2747.990 (96.90)	96.6	(92.3, 101.0)
C_{max} (ng/mL)	589.4046 718.244 (59.85)	607.8288 701.049 (51.08)	97.0	(89.8, 104.8)
T_{max}[3] (h)	2.84 (1.00, 4.67)	2.67 (1.00, 5.50)		
$T_{½}$[4] (h)	1.555 (70.34)	1.732 (63.20)		

[1]Treatment (M) = Single oral dose of Omeprazole Magnesium Delayed Release 20mg Tablets (Dr. Reddy's Laboratories Inc.)
[2] Treatment (S) = Single oral dose of LOSEC™ 20 mg Delayed Release Tablets (AstraZeneca Canada Inc, Canada); purchased in Canada
[3]For T_{max} Median (range) is presented
[4] For $T_{½}$ arithmetic mean (CV%) is presented

A blinded, randomized, single oral dose, two way crossover comparative bioavailability study of Omeprazole Magnesium Delayed Release Tablets, 20 mg (Dr. Reddy's Laboratories Inc.) and PrLOSEC® (omeprazole magnesium) delayed release tablets 20 mg (AstraZeneca Canada Inc.) was conducted in 35 healthy, adult, male volunteers under fed conditions. The results are presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Omeprazole (1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Least Square Means	90% Confidence Interval
AUC_T (ng.hr/mL)	2842.5743 3719.779 (71.67)	3047.4896 4081.471 (70.17)	93.3	(85.3, 102.0)
AUC_I (ng.hr/mL)	2881.5227 3763.961 (71.51)	3087.9181 4127.839 (70.09)	93.3	(85.4, 101.9)
C_{max} (ng/mL)	1023.2683 1100.126 (37.57)	1057.3648 1179.087 (44.49)	96.8	(86.1, 108.8)
T_{max}[3] (h)	7.00 (3.50, 14.00)	6.50 (2.50, 11.00)		
$T_{½}$[4](h)	2.115 (55.47)	2.129 (57.51)		

[1]Treatment (R) = Single oral dose of Omeprazole Magnesium Delayed Release 20mg Tablets (Dr. Reddy's Laboratories Inc.)
[2] Treatment (D) = Single oral dose of LOSEC™ 20 mg Delayed Release Tablets (AstraZeneca Canada Inc, Canada); purchased in Canada
[3]For T_{max} Median (range) is presented
[4] For $T_{½}$ arithmetic mean (CV%) is presented

TOXICOLOGY

Acute Toxicity

Table 4 Acute Toxicity Studies of Omeprazole.

(q) SPECIES	**(r) SEX**	**(s) ROUTE**	**(t) LD_{50} (u) (mg/kg)**
Mouse	M	p.o.[1*]	> 4000
	F	p.o.[1*]	> 4000
Mouse	M	p.o.[1]	1520
	F	p.o.[1]	1380
Mouse	M	i.v.	83
	F	i.v.	> 100

(q) SPECIES	(r) SEX	(s) ROUTE	(t) LD_{50} (u) (mg/kg)
Rat	M	p.o.[1*]	> 4000
	F	p.o.[1*]	> 4000
Rat	M	p.o.[1]	> 5010
	F	p.o.[1]	3320
Rat	M	i.v.	> 40
	F	i.v.	> 40

1 suspension in Methocel®, not buffered * non-micronized test compound

The highest oral dose (4000 mg/kg) of non-micronized omeprazole did not cause death in any of the species tested. With micronized omeprazole, suspended in Methocel®, the acute oral LD_{50} was approximately 1500 mg/kg in mice; in male rats, higher than the maximum dose (5000 mg/kg); and in female rats, approximately 3000 mg/kg. As much as 80% of the compound may not have been absorbed due to acid degradation of these single doses in the stomach. Death occurred within 2 days of ingestion and was preceded by reduced motor activity, reduced respiration frequency but increased respiration depth, reduced body temperature, and twitching, tremor or convulsions. The highest oral dose given to dogs (660 mg/kg) caused vomiting within 40-100 minutes of ingestion. The acute intravenous LD_{50} was 83 mg/kg in male mice, and in female mice >100 mg/kg. The corresponding figure in rats was >40 mg/kg. Death occurred within a few minutes of injection, preceded by cyanosis and convulsions.

Long-Term General Toxicity

The general, long-term toxicity of omeprazole was studied in mice, rats and dogs after oral and intravenous administration. Mice received oral doses of 14-140 mg/kg for up to 18 months, rats 14-400 mg/kg for up to 24 months, and dogs 1-140 mg/kg for up to 12 months. Intravenous omeprazole was given to rats in doses of 2-16 mg/kg for up to one month and to 10 dogs in doses of 1-9 mg/kg for up to one month.

In the dog, a slight to moderate atrophy of the chief cells and rugal hypertrophy were observed. These changes were reversible after treatment cessation.

Following chronic intravenous administration of omeprazole to rats (~1.7-15.5 mg/kg/day) for one month and to dogs (~0.7-8.6 mg/kg/day) for one month, no treatment-related changes were observed.

In the rat, decreased plasma concentrations of triiodothyronine were observed in the two highest groups; TSH increased in the high-dose males. Lower doses had no significant effect. General

hypertrophy of the oxyntic mucosa was found; the size of some chief cells was decreased and some granularity was observed. Both the hypertrophy and chief cell changes were reversible.

Reproduction Studies
In studies with male and female rats given oral doses of up to 138 mg/kg/day (approximately 500 times the recommended human dose), fertility and reproductive performance were not affected.

In rabbits, increased embryo-lethality and fetal resorption were observed at maternotoxic doses of 69 and 138 mg/kg/day (250 and 500 times the human dose). No maternal or fetal toxicity was observed in pregnant rats treated at doses ranging from 13.8 to 138 mg/kg/day (50 to 500 times the human dose). In rats, a slight decrease in litter size at birth and slightly impaired postnatal viability and growth were observed in offspring resulting from parents treated with high doses of 138 mg/kg/day (500 times the human dose) of omeprazole. Similar effects were not seen at lower doses.

Mutagenicity
Omeprazole was tested *in vivo* (mouse micronucleus test, chromosome aberration in mice) and *in vitro* (Ames test, mouse lymphoma forward mutation assay), and showed no evidence of a mutagenic effect.

Carcinogenicity
An 18-month oral study was conducted in mice at doses of 14, 44 and 140 mg/kg/day. No evidence of carcinogenic potential was seen. A 24-month oral study was conducted in rats at doses of 14, 44 and 140 mg/kg/day. No increase in carcinomas was observed in any organ. However, there were dose- and time-dependent increases of tumour-like proliferations in the stomach. Histology showed a continuum from diffuse ECL-cell hyperplasia in the basal region of the gastric glands to less frequent micronoduli and occasional tumour-like proliferations, some extending into the sub-mucosa. The proliferations were classified as gastric carcinoids. The proliferation of ECL-cells and development of carcinoids were more frequent in female rats.

No metastases were identified in any of the animals. Carcinoids have not been observed after long-term administration of omeprazole to mice and dogs.

Gastric ECL-Cell Carcinoids
Extensive investigations have been carried out to explain the ECL-cell hyperplasia and the gastric carcinoid findings in rats. Gastrin produced by the G-cells in the antrum plays an important role in the feedback control of gastric acid secretion.

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 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 H_2-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 H_2-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 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 recovered to normal during the next 12 months of no treatment.

No carcinoids have been found in mice, and in dogs following administration of 28 mg/kg/day for 7 years.

Investigation in man has demonstrated an initial moderate increase in gastrin levels during treatment with omeprazole, but no further increase occurred during long-term (up to 3 years) treatment. No significant changes have been found in the endocrine cells of the oxyntic gastric mucosa during short- or long-term treatment with omeprazole in man, to date. Chronic treatment of patients with Zollinger-Ellison syndrome with mean daily doses of omeprazole of 60 mg/day for up to 5 years has not influenced the pre-treatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

BIBLIOGRAPHY

1. AB Astra.
Omeprazole Monograph. Oxford Clinical Communications, 1988.

2. Alumets J, El Munshid HA, et al.
Effect of antrum exclusion on endocrine cells of rat stomach.
J Physiol 1979;286:145-155.

3. Andersson T.
Pharmacokinetics, metabolism and interactions of acid pump inhibitors.
Clin Pharmacokinet 1996;31:9-28.

4. Bardhan KD, Bianchi Porro G, Bose K, et al.
A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. J Clin Gastroenterol 1986;8(4):408-413.

5. Brunner G, Creutzfeldt W.
Omeprazole in the long-term management of patients with acid-related diseases resistant to ranitidine. Scand J Gastroenterol 1989;24(Suppl 166):101-105.

6. Cederberg C, Ekenved G, et al.
Acid inhibitory characteristics of omeprazole in man. Scand J Gastroenterol 1985;20(108):105-112.

7. Clissold SP, Campoli-Richards DM.
Omeprazole - a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. Drugs 1986;32:15-47.

8. Ekman L, Hansson E, et al.
Toxicological studies on omeprazole. Scand J Gastroenterol 1985;20(108):53-69.

9. Hameeteman W, Tytgat GN.
Healing of chronic Barrett ulcers with omeprazole. Am J Gastroenterol 1986;81:764-766.

10. Howden CW, Payton CD, et al.
Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure. Eur J Clin Pharmacol 1985;28:637-640.

11. Labenz J, Ruhl GH, Bertrams J, Borsch G.

Medium- or high-dose omeprazole plus amoxicillin eradicates *Helicobacter pylori* in gastric ulcer disease. Am J Gastroent 1994;89(5):726-730.

12. Lamberts R, et al.
Long-term omeprazole treatment in man. Effects on gastric endocrine cell population. Digestion 1988;39:126-135.

13. Lind T.
Bioavailability and effect on acid secretion during repeated administration of omeprazole, 20 mg o.m. - comparison between an enteric coated tablet and enteric coated granule formulation. Astra Report No. I-386 1992-09-07 (Data on file).

14. Lind T, et al.
Eradication of *Helicobacter pylori* using one week triple therapies combining omeprazole with two antimicrobials: The MACH1 study. Helicobacter 1996;1(3):138-144.

15. Lloyd-Davies KA, et al.
Omeprazole in the treatment of ZES: a 4 year international study.
Alimentary Pharmacol and Ther 1988;2:13-32.

16. Logan RPH, Bardhan KD, et al.
Eradication of *Helicobacter pylori* and prevention of recurrence of duodenal ulcer: a randomized, double-blind, multi-centre trial of omeprazole with or without clarithromycin. Aliment Pharmacol Ther 1995;9:417-423.

17. McArthur KE, Collen MJ, et al.
Omeprazole: Effective, convenient therapy for Zollinger-Ellison Syndrome.
Gastroenterology 1985;88:939-944.

18. Regardh CG, Gabrielsson M, et al.
Pharmacokinetics and metabolism of omeprazole in animals and man - an overview.
Scand J Gastroenterol 1985;20(108):79-94.

19. Thomson ABR.
Twenty-four-hour gastric pH and pharmacokinetics during treatment with the new omeprazole

20 mg enteric coated tablet and the commercially available Losec® 20 mg capsule in duodenal ulcer patients. Astra Report No. I-1219 1994-05-16 (Data on file).

20. Wallmark B, Lindberg P.
Mechanism of action of omeprazole. ISI Atlas of Science: Pharmacology 1987;1:158- 160.

21. PrLOSEC® omeprazole magnesium delayed release tablets, 20 mg omeprazole (as omeprazole magnesium), submission control 240173, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. October 30, 2020.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]Omeprazole Magnesium Delayed Release Tablets
20 mg omeprazole (as omeprazole magnesium)

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

What is Omeprazole Magnesium Delayed Release Tablets used for?
Omeprazole Magnesium Delayed Release Tablets are used to treat problems caused by too much acid in the stomach such as:

- stomach ulcers (sores).
- duodenal ulcers (sores on the first part of the intestine).
- stomach and duodenal ulcers caused by a bacterium, *Helicobacter pylori*.
- reflux esophagitis (tissue damage caused by stomach acid and juices moving up the food tube).
- symptoms of reflux disease (e.g. heartburn, backup of stomach contents to the throat).
- ulcers caused by nonsteroidal anti-inflammatory drugs (drugs for pain and sore joints).
- dyspepsia, a group of symptoms which may include stomach pain / discomfort, heartburn and backup of stomach contents to the throat. Dyspepsia can be caused by the other conditions in this list.
- a rare condition where the stomach produces too much acid (Zollinger-Ellison syndrome).

How does Omeprazole Magnesium Delayed Release Tablets work?
Omeprazole Magnesium Delayed Release Tablets are a medicine called a proton pump inhibitor (PPI). Omeprazole Magnesium Delayed Release Tablets works by reducing the amount of acid made in your stomach.

What are the ingredients in Omeprazole Magnesium Delayed Release Tablets?
Medicinal ingredients: omeprazole magnesium

Non-medicinal ingredients: hypromellose, iron oxide black and iron oxide red, lecithin, mannitol, meglumine, methacrylic acid copolymer dispersion, polyethylene glycol, simethicone emulsion, shellac glaze, sodium hydroxide, sodium starch glycolate, sodium stearyl fumarate, talc and titanium dioxide.

Omeprazole Magnesium Delayed Release Tablets comes in the following dosage forms:
Tablets of omeprazole 20 mg.

Do not use Omeprazole Magnesium Delayed Release Tablets if:

- you are allergic to omeprazole, substituted benzimidazoles or any of the other ingredients in Omeprazole Magnesium Delayed Release Tablets (see "What are the ingredients in Omeprazole Magnesium Delayed Release Tablets?").
- you are taking rilpivirine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Omeprazole Magnesium Delayed Release Tablets. Talk about any health conditions or problems you may have, including if you:

- have had any health problems in the past.
- have severe liver problems now or have had in the past.
- are pregnant or plan to become pregnant.
- are breastfeeding or planning to breastfeed, as omeprazole is excreted in breast milk.
- take any other medications, including ones you can buy without a prescription.
- are due to have a specific blood test (Chromogranin A).

Other warnings you should know about:
Omeprazole Magnesium Delayed Release Tablets are not recommended for use in patients under 18 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.

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

Tell your doctor or pharmacist about symptoms that may be a sign of a more serious problem in your stomach or intestine such as:

- trouble swallowing.
- unplanned weight loss.
- vomiting blood or food.
- black (blood-stained) stools.

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

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

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

Using Omeprazole Magnesium Delayed Release Tablets for a long period of time may 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 Omeprazole Magnesium Delayed Release Tablets:

- medication for HIV: Omeprazole Magnesium Delayed Release Tablets may decrease the effectiveness of some drugs used for HIV treatment; atazanavir, nelfinavir, and saquinavir should not be used with Omeprazole Magnesium Delayed Release Tablets.
- a high-dose of methotrexate (a drug used in high doses to treat cancer): Omeprazole Magnesium Delayed Release Tablets may need to be temporarily withdrawn.
- clopidogrel, which is used for the prevention of blood clots: Omeprazole Magnesium Delayed Release Tablets may interact with this drug, therefore use with clopidogrel should be avoided.
- Drug effects may be influenced if Omeprazole Magnesium Delayed Release Tablets are taken at the same time as some drugs used to prevent fungal infections (itraconazole, ketoconazole, voriconazole), anxiety (diazepam), epilepsy (phenytoin), blood clotting (warfarin or other vitamin K blockers), transplant rejection (tacrolimus), poor circulation in the legs (cilostazol)*, heart problems (digoxin), treatment for tuberculosis (rifampin), St John's Wort (Hypericum perforatum) or a certain type of anticancer drug (erlotinib or any other anticancer drug from the same class).

* not marketed in Canada

How to take Omeprazole Magnesium Delayed Release Tablets:
Follow your doctor's directions carefully. They may be different from the information contained in this leaflet.

- Take all doses of Omeprazole Magnesium Delayed Release Tablets that your doctor prescribes even when you feel well. Doses every day are needed to help damaged areas heal.
- If you take Omeprazole Magnesium Delayed Release Tablets with antibiotic drugs, it is important that you take all medications at the right time of day for the whole treatment

period. Studies have shown that patients who take their medications as prescribed have better ulcer healing rates and greater success getting rid of their *H. pylori* infection.

- Take Omeprazole Magnesium Delayed Release Tablets until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if Omeprazole Magnesium Delayed Release Tablets are stopped too soon. Omeprazole Magnesium Delayed Release Tablets needs to be taken for the full treatment to help correct acid problems.
- Omeprazole Magnesium Delayed Release Tablets may be taken with food or on an empty stomach.
- Do not chew or crush your Omeprazole Magnesium Delayed Release Tablets. Swallow the tablet whole with half a glass of water.

Usual dose:

Your doctor may tell you to take Omeprazole Magnesium Delayed Release Tablets:

- 20-40 mg once a day for 2-8 weeks to heal damaged areas.
- 20-40 mg to control symptoms of reflux disease or to stop reflux esophagitis from coming back.
- 20 mg to stop ulcers from returning while you take your medicine for pain and joint problems.
- 60 mg once a day to treat Zollinger-Ellison syndrome
- In combination with antibiotic drugs for one week to treat ulcers caused by *Helicobacter pylori*.

    - as Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is omeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days.
    - or as Omeprazole, Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg, all twice daily for seven days.
    - If your ulcer is bothering you, your doctor may recommend further treatment with Omeprazole Magnesium Delayed Release Tablets to make sure that your ulcer is healed.

Overdose:

If you think you, or a person you are caring for, have taken too much Omeprazole Magnesium Delayed Release Tablets, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of Omeprazole Magnesium Delayed Release Tablets and remember within 12 hours, take it as soon as possible. Then go back to your regular schedule. However, if more than 12 hours have passed when you remember, do not take the missed tablet. Do not double the dose. Just take your next dose on time.

What are possible side effects from using Omeprazole Magnesium Delayed Release Tablets?

Like all medicines, Omeprazole Magnesium Delayed Release Tablets may cause side effects in some people. Side effects are usually mild and go away a short time after starting Omeprazole Magnesium Delayed Release Tablets.

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

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

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

Common side effects (≥ 1 in 100 patients):

- Headache.
- Diarrhea.
- Constipation.
- Abdominal pain.
- Nausea/ vomiting.
- Excess gas in stomach (flatulence).

Uncommon side effects (≥ 1 in 1000 patients, but < 1 in 100 patients):

- Dizziness.
- Feeling like you or your surroundings are moving (vertigo).
- Difficulty sleeping.
- Feeling sleepy.
- Sensation of burning/ prickling/ numbness.

Rare side effects (< 1 in 1000 patients):

- Dry mouth.
- Hair loss.
- Increased sweating.
- Taste disorders.

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 Omeprazole Magnesium Delayed Release Tablets.

Serious side effects and what to do about them			
Symptom/ effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON (≥ 1 in 1000 patients, but < 1 in 100 patients)			
skin reactions (such as skin rash, dermatitis, itchy skin and/or hives)		X	
feeling ill		X	
RARE (≥ 1 in 10 000 patients, but < 1 in 1000 patients)			
inflammation in the mouth		X	
gastrointestinal fungal infection		X	
inflammation of the kidney		X	
liver problems, ie, inflammation of the liver with or without jaundice, impaired liver function			X
blood disorders (reduced number of cells in the blood, low blood sodium)		X	
inflammation in the gut (leading to diarrhea)		X	
sore joints and muscles		X	
muscular weakness		X	
development of breasts in males		X	
sensitivity to sunlight		X	
severe skin reactions			X
hypersensitive (allergic) reactions (such as swelling of tissues, fever, discomfort / tightness in chest and anaphylactic shock)			X
blurred vision		X	
if you already have severe liver disease, you may experience disorientation / aggression /		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
confusion / decreased consciousness			
if you are very ill, you may feel confused, nervous, depressed or hallucinate		X	
VERY RARE (< 1 in 10 000 patients)			
low blood magnesium[0] (which may result in low blood calcium and / or low blood potassium)		X	

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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional. Other situations may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using Omeprazole Magnesium Delayed Release Tablets.

Reporting Side Effects

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

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

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

Storage:
Keep all tablets sealed in the bottle until it is time for a dose. If you do not, moisture from the air may damage the tablets.

Keep the pack at room temperature 15°C to 30°C. Do not keep Omeprazole Magnesium Delayed Release Tablets in the bathroom medicine cabinet or other warm, moist places.

Do not use Omeprazole Magnesium Delayed Release Tablets after the expiry date marked on the pack.

Keep out of sight and reach of children.

If you want more information about Omeprazole Magnesium Delayed Release Tablets:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.drreddys.com, or by contacting 1-855-845-1739.

NOTE: This PATIENT MEDICATION INFORMATION leaflet provides you with the most current information at the time of printing.

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