PRODUCT MONOGRAPH

[Pr] OMEPRAZOLE

omeprazole delayed release capsules USP

10 mg and 20 mg omeprazole

H^+, K^+-ATPase Inhibitor

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omeprazole delayed release capsules USP

10 mg and 20 mg omeprazole

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

ACTIONS AND CLINICAL PHARMACOLOGY

Omeprazole inhibits the gastric enzyme H+,K+-ATPase (the proton pump) which catalyzes the exchange of H+ and K+. It 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. A mean reduction of 24-hour intragastric acidity of approximately 80% was achieved during repeated dosing of 20 mg daily.

Omeprazole is absorbed rapidly. After an initial oral dose of omeprazole, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. Peak plasma levels occur within about four hours.

The terminal plasma half-life is about 40 minutes. 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.

The 20 mg tablet and the 20 mg capsule are not bioequivalent in terms of plasma omeprazole AUC, C_{max} and $t_{max.}$ Omeprazole 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 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 IV and oral administration 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 (omeprazole) is 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;
- Zollinger-Ellison Syndrome (Pathological hypersecretory condition).

CONTRAINDICATIONS

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

Co-administration with rilpivirine is contraindicated.

WARNINGS

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with OMEPRAZOLE is instituted, as treatment with omeprazole 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 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 should not exceed 20 mg daily (see REYATAZ Product Monograph).

Saquinavir:
If omeprazole 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. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

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

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

Use in Pregnancy
The safety of omeprazole in pregnancy has not been established. OMEPRAZOLE should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Mothers
Omeprazole is secreted in breast milk. OMEPRAZOLE should not be given to nursing mothers unless its use is considered essential.

Use in Children
The safety and effectiveness of omeprazole in children has not yet been established.

PRECAUTIONS

General
***Clostridium Difficile* Associated Diarrhea**
Decreased gastric acidity due to any means, including any proton pump inhibitor, 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.

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). 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). Twenty mg given once daily to these patients for four 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 (see DOSAGE AND ADMINISTRATION).

Carcinogenicity

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 seven 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- and long-term treatment in a limited number of patients for up to six years has 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 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.

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 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 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 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 3760 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 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 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 versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on any 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 IV 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 of pretreatment 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 concomitantly administered antacids has been found.

Food
No interaction with food 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 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 there has been no consistent relationship with the treatment. Adverse events have been recorded during controlled clinical investigations in 2764 patients exposed to omeprazole 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 the placebo group. 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 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 one percent) have been reported in individuals receiving omeprazole therapy 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: <1/10,000.

Central and Peripheral Nervous System: Common: headache. Uncommon: dizziness, paraesthesia, somnolence, insomnia and vertigo. Rare: reversible mental confusion, agitation, aggression, depression and hallucinations, 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 urticaria. 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, 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).

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).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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).

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 two weeks. For patients not healed after this initial course of therapy, an additional two weeks of treatment is recommended.

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

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

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

NSAID-Associated Gastric or Duodenal Ulcers
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 four weeks. For those patients not healed after this initial course of therapy, an additional four 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 six months.

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

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

Maintenance Therapy for Reflux Esophagitis: For the long-term management of patients with healed reflux esophagitis, 10 mg omeprazole once daily has been found to be effective in controlled clinical trials of 12 months' duration, and in continuous maintenance treatment in a limited number of patients for a period of up to six years. In the case of recurrence, the dose can be increased to 20-40 mg omeprazole.

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 four weeks, further investigation is recommended. Since some patients respond adequately to 10 mg given once daily, individual dose adjustment should be considered. For the maintenance of symptom relief in patients with gastroesophageal reflux

disease (i.e., heartburn and regurgitation), the recommended adult dose is 10 mg given once daily.

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 the patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20 mg to 120 mg 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 TID 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 capsules should be swallowed whole with sufficient water. The capsules must not be chewed or crushed.

PHARMACEUTICAL INFORMATION

Drug Substance

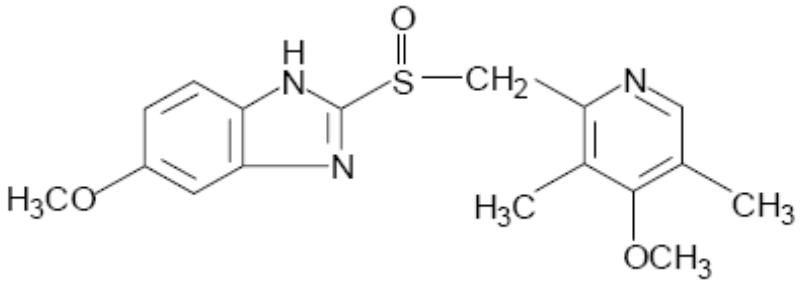
Proper Name: omeprazole

Chemical Name: 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl}-H-benzimidazole.

Molecular Formula: $C_{17}H_{19}N_3O_3S$

Molecular Mass: 345.42 g/mol

Structural Formula:



Physicochemical properties:

Omeprazole is a non-hygroscopic, crystalline substance which melts with decomposition at about 150°C. The substance is slightly soluble in water. The pKa of the benzimidazole is 8.8 and that of the pyridinium ion, 4.0.

COMPOSITION

In addition to omeprazole, each capsule contains the nonmedicinal ingredients: carrageenan, croscarmellose sodium, dibutyl sebacate, hypromellose, hypromellose phthalate, iron oxide red, lactose anhydrous, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, polysorbate 80, potassium chloride, povidone, talc, titanium dioxide, water.

STABILITY AND STORAGE RECOMMENDATIONS

Store bottle tightly capped between 15°C and 30°C. Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

10 mg Capsule
HPMC capsule filled with pellets. Each two-piece capsule consists of a pink cap imprinted with OME 10 and a pink body imprinted with OME 10.

20 mg Capsule
HPMC capsule filled with pellets. Each two-piece capsule consists of a dark pink cap imprinted with OME 20 and a pink body imprinted with OME 20.

OMEPRAZOLE capsules are available in the following formats:

10 mg Capsules: Bottles of 28, 30 and blisters of 28 (4x7) capsules.

20 mg Capsules: Bottles of 30, 100, 500 and 1000 and blisters of 28 (4x7) capsules.

CLINICAL TRIALS

Comparative Bioavailability

Two comparative randomized, single-dose, 2-way, crossover bioavailability studies were performed using healthy male human volunteers under fasting conditions and fed conditions. The rate and extent of absorption of omeprazole following a single 20 mg (1x20 mg capsule) oral dose of OMEPRAZOLE and LOSEC were measured and compared. The results from measured data are summarized as follows:

Fasted Study

Twenty-eight healthy non-smoking adult male volunteers were enrolled in the study, and all 28 subjects completed the clinical phase of the study. The statistical and pharmacokinetic analyses were performed based on 28 subjects.

Omeprazole in Plasma
(1 x 20 mg)
From measured data for fasted condition
Geometric Least-Square Means
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Least-Square Means	90% Confidence Interval
AUC_T (ng·h/mL)	296.73 397.2 (95.4)	343.14 465.9 (97.5)	86.5	81.4 – 91.9
AUC_I (ng·h/mL)	311.50 427.9 (92.2)	355.23 508.6 (94.0)	87.7	81.5 – 94.3
C_{max} (ng/mL)	172.7812 216.811 (75.2)	212.7105 268.754 (72.6)	81.2	69.7 – 94.7
T_{max}§ (h)	2.1654 (57.9)	1.8113 (51.4)		
$T_{½}$§ (h)	0.7847 (30.0)	0.7919 (33.5)		

*Omeprazole 20 mg capsules manufactured for Sivem Pharmaceuticals ULC.
† Losec® 20 mg capsules manufactured by AstraZeneca Canada Inc., were purchased in Canada.
§ Expressed as either the arithmetic mean (CV%) only

Fed Study
Twenty-eight healthy non-smoking adult male volunteers were enrolled in the study, and 27 of 28 subjects completed the clinical phase of the study. The statistical and pharmacokinetic analyses were performed on 27 subjects.

Omeprazole in Plasma (1 x 20 mg) From measured data for fed condition Geometric Least-Square Means Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Least-Square Means	90% Confidence Interval
AUC_T (ng·h/mL)	468.550 660.32 (95.9)	486.153 605.56 (86.9)	96.4	80.3 – 115.7
AUC_I (ng·h/mL)	517.926 736.10 (95.4)	494.802 696.26 (99.4)	104.7	93.1 – 117.7
C_{max} (ng/mL)	207.0112 263.989 (60.8)	179.0558 220.544 (59.7)	115.6	91.8 – 145.6
T_{max}§ (h)	5.2766 (24.2)	5.1776 (34.6)		
$T_{½}$§ (h)	1.2470 (45.2)	1.2198 (62.7)		

*Omeprazole 20 mg capsules manufactured for Sivem Pharmaceuticals ULC.
† Losec® 20 mg capsules manufactured by AstraZeneca Canada Inc., were purchased in Canada.
§ Expressed as either the arithmetic mean (CV%) only

PHARMACOLOGY

Animal Pharmacology
Pharmacodynamics
Omeprazole differs from existing inhibitors of gastric acid secretion such as histamine H_2-receptor antagonists or 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 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 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 one 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 postdose 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.

Table 1 Percentage inhibition of mean acid output after single oral doses of omeprazole.

STIMULUS	TYPE OF SUBJECT	OMEPRAZOLE DOSE		TIME AFTER DOSE (h)
		20 mg	80 mg	
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 oral dosing with 20 mg of omeprazole once daily provided rapid inhibition of gastric acid secretion, with the maximum effect achieved within the first four days of treatment. Gastric emptying was unaffected by omeprazole.

In duodenal ulcer patients, a mean decrease in 24-hour intragastric acidity of about 80% was then maintained. The mean decrease in peak acid output after pentagastrin stimulation was about 70% 24 hours after repeated dosing with omeprazole 20 mg. Omeprazole caused a transient decrease in stimulated pepsin output which resolved within four hours of dosing. Omeprazole had no effect on intrinsic factor secretion.

Other Pharmacodynamic Effects

The effect of omeprazole on various organ systems has been investigated. **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 is rapidly absorbed. After an initial oral dose of omeprazole, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy, the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. After oral administration, peak plasma levels occur within about four hours. The terminal plasma half-life is approximately 40 minutes; the total plasma clearance is 0.6 L/min. Although 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.

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.

Following IV and oral administration, 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). 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. However, patients with impaired liver function showed increased bioavailability (75%), reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours). Twenty mg given once daily to these patients for four 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).

TOXICOLOGY

Acute Toxicity

Table 2 Acute toxicity studies of omeprazole

Species	SEX	ROUTE	LD_{50} (MG/KG)
Mouse	M	PO[1]*	>4000
	F	PO[1]*	>4000
Mouse	M	PO[1]	1520
	F	PO[1]	1380
Mouse	M	IV	83
	F	IV	>100
Rat	M	PO[1]*	>4000
	F	PO[1]*	>4000
Rat	M	PO[1]	>5010
	F	PO[1]	3320
Rat	M	IV	>40
	F	IV	>40

[1] suspension of 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 two 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 dogs 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 submucosa. 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 seven 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 three 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 five years has not influenced the pretreatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

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

[Pr]OMEPRAZOLE
omeprazole delayed release capsules USP

Read this carefully before you start taking OMEPRAZOLE 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.

What is OMEPRAZOLE used for?
OMEPRAZOLE is 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)
- ulcers caused by nonsteroidal anti-inflammatory drugs (drugs for pain and sore joints)
- reflux esophagitis (tissue damage caused by the stomach acid and juices moving up the food tube)
- symptoms of reflux disease (e.g., heartburn, backup of stomach contents to the throat)
- a rare condition where the stomach produces too much acid (Zollinger-Ellison syndrome)

How does OMEPRAZOLE work?
OMEPRAZOLE is a medicine called a proton pump inhibitor (PPI). OMEPRAZOLE works by reducing the amount of acid made in your stomach.

What are the ingredients in OMEPRAZOLE?
Medicinal ingredients: omeprazole

Non-medicinal ingredients: carrageenan, croscarmellose sodium, dibutyl sebacate, hypromellose, hypromellose phthalate, iron oxide red, lactose anhydrous, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, polysorbate 80, potassium chloride, povidone, talc, titanium dioxide, water.

Check with your doctor if you think you might be allergic to any of the above ingredients.

OMEPRAZOLE comes in the following dosage forms:
Capsules of omeprazole 20 mg

Do not use OMEPRAZOLE if:
- you are allergic to omeprazole, substituted benzimidazoles or any of the other ingredients in OMEPRAZOLE (see "What are the ingredients in OMEPRAZOLE?").
- you are taking rilpivirine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OMEPRAZOLE. 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 it 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 is 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.

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 B_{12} from the diet.
This may cause a shortage of Vitamin B_{12} in your body. Talk to your doctor about this risk.

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

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

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

The following may interact with OMEPRAZOLE:

- medication for HIV: OMEPRAZOLE may decrease the effectiveness of some drugs used for HIV treatment; atazanavir, nelfinavir and saquinavir should not be used with OMEPRAZOLE;
- a high-dose of methotrexate (a drug used in high doses to treat cancer). OMEPRAZOLE may need to be temporarily withdrawn.
- clopidogrel, which is used for the prevention of blood clots. OMEPRAZOLE may interact with this drug, therefore use with clopidogrel should be avoided.
- Drug effects may be influenced if OMEPRAZOLE is 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:

Follow your doctor's directions carefully. They may be different from the information contained in this leaflet.

- Take all doses of OMEPRAZOLE that your doctor prescribes, even when you feel well. Doses every day are needed to help damaged areas heal.
- Take OMEPRAZOLE until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if OMEPRAZOLE is stopped too soon. OMEPRAZOLE needs to be taken for the full treatment to help correct acid problems.
- OMEPRAZOLE may be taken with food or on an empty stomach.
- Do not chew or crush your OMEPRAZOLE capsules. Swallow the capsule whole with half a glass of water.

Usual dose:

Your doctor may tell you to take OMEPRAZOLE:

- 10-40 mg once a day for 2-8 weeks to heal damaged areas.
- 10-40 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.

Overdose:

If you think you have taken too much OMEPRAZOLE, contact your 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 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 dose. Do not double the dose. Just take your next dose on time.

What are possible side effects from using OMEPRAZOLE?

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

These are not all the possible side effects you may feel when taking OMEPRAZOLE. 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 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.

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, i.e., inflammation of the liver with or without jaundice, impaired liver function			**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**	
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/ confusion/ decreased consciousness		**X**	
if you are very ill, you may feel confused, nervous, depressed or hallucinate		**X**	
VERY RARE (< 1 in 10,000 patients)			
low blood magnesium[θ] (which may result in low blood calcium and/or low blood potassium)		**X**	

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

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

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

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

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

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

Remember to keep OMEPRAZOLE well out of sight and reach of children. Keep the package at room temperature (15-30°C). Do not keep OMEPRAZOLE in the bathroom medicine cabinet or other warm, moist places.

Do not use OMEPRAZOLE after the expiry date marked on the pack.

Keep out of sight and reach of children.

If you want more information about OMEPRAZOLE:

- 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.html); or by contacting the sponsor, Sivem Pharmaceuticals ULC, at: 1-855-788-3153.

Or at: www.sivem.ca

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

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