PRODUCT MONOGRAPH

^{Pr}Q-OMEPRAZOLE

(omeprazole delayed release capsules, USP)

10 mg and 20 mg omeprazole

H^+, K^+-ATPase Inhibitor

QD Pharmaceuticals ULC
85 Advance Road
Toronto ON
M8Z 2S6

Date of Revision:
May 4, 2015

Submission Control Number: 183451

PRODUCT MONOGRAPH

PrQ-OMEPRAZOLE

(omeprazole delayed release capsules, USP)

10 mg and 20 mg omeprazole

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^+. 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.

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 ulcers, 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, reducing the need for prolonged antisecretory 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 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 omeprazole capsule (as a multiple unit formulation) is usually emptied gradually from the stomach into the intestine.

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. and oral administration of omeprazole, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces.

INDICATIONS AND CLINICAL USE

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);
- eradication of *Helicobacter pylori* (*H. pylori*).

Omeprazole, 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.

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).

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.

Table 1 Results of studies in patients with a history of duodenal ulcer who were *H. pylori* -positive.

	Treatment	Eradication Rate	
		APT or ITTAnalysis	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 posttreatment,
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 2 Results of studies in patients with active peptic ulcer who were *H. pylori* positive (ITT analysis).

	Treatment	Eradication Rate (PP Analysis)	Ulcer Healing Rate (Post Treatment)	Rate of Patients in Remission (6 months after cessation 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).

CONTRAINDICATIONS

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

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.

Concomitant administration with atazanavir and nelfinavir is not recommended (see PRECAUTIONS, Drug Interactions).

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).

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

It is not known if omeprazole is secreted in human 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

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.

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 may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella, Campylobacter* and possibly *Clostridium difficile*.

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 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 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.

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.

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 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).

Antiretroviral Drugs

Omeprazole, like other acid-reducing agents, has 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 interaction mechanisms are via CYP 2C19.

Reports indicate that omeprazole has a significant impact on atazanavir exposure, decreasing AUC, C_{max} and $C_{min.}$ This interaction is only partially overcome by the addition of ritonavir to the atazanavir treatment regimen. Similarly, decreased serum levels of nelfinavir have also been reported when given together with omeprazole. Concomitant administration of omeprazole with atazanavir and nelfinavir is therefore not recommended. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs where unchanged serum levels have been reported when given with omeprazole (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 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.

Laboratory Tests

During treatment with antisecretory drugs 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. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalized by this time.

Other Interactions

As demonstrated with other PPIs, prolonged use may impair the absorption of protein-bound Vitamin B_{12} and may contribute to the development of Vitamin B_{12} deficiency.

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: <1/10000.

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).

***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%).

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

No information is available on the effects of higher doses in man and specific recommendations for treatment cannot be given. Single oral doses of up to 400 mg of omeprazole have not resulted in any severe symptoms and no specific treatment has been needed. 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.

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.

Maintenance Therapy for Duodenal Ulcer: Over 95% of duodenal 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 dose is 10 mg once daily, increased to 20-40 mg once daily, as necessary.

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.

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 dose is 20 mg once daily, increased to 40 mg once daily, as necessary.

NSAID-Associated Gastric or Duodenal Ulcers

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

Acute Therapy: In patients with NSAlD-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

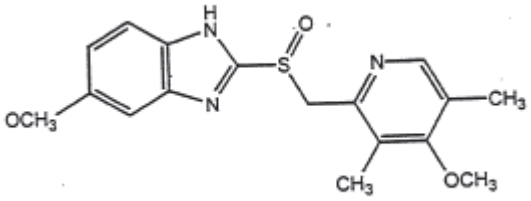
be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered.

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.

PHARMACEUTICAL INFORMATION

Drug Substance	
Proper name	omeprazole
Chemical Name	1*H*-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl]sulfinyl]-. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]benzimidazole
Structural Formula	
Molecular Formula	$C_{17}H_{19}N_3O_3S$
Molecular Weight	345.42 g/mol
Description	Omeprazole is a nonhygroscopic, crystalline substance which melts with decomposition at between 150ºC and 160ºC. The substance is soluble in dichloromethane, sparingly soluble in methanol and in alcohol and very slightly soluble in water. The pKa of the benzimidazole is 8.8 and that of the pyridinium ion, 4.0.

Composition

Active: Omeprazole

Nonmedicinal ingredients:

Composition of 10 and 20 mg Capsule Fill

Sugar spheres

*Surelease® E-7-7050 (ethyl cellulose aqueous dispersion)

Talc

Methacrylic acid copolymer dispersion (Eudragit L 30 D)

Triethyl citrate (Eudraflex)

Hydroxypropylmethyl cellulose (hypromellose 2910)

Titanium dioxide

Composition of Capsule Shells for 10 mg and 20 mg capsules

FDA/E172 Red Iron Oxide

Titanium Dioxide

Gelatin

*Surelease® E-7-7050 solids consists of ethylcellulose, dibutyl sebacate, oleic acid, fumed silica and ammonium hydroxide.

Stability and Storage Recommendations

Store between 15 C and 25 C. Protect from light and moisture

AVAILABILITY OF DOSAGE FORMS

Q-OMEPRAZOLE 10 mg delayed release capsules, USP, are no. 3, dark pink opaque cap / dark pink opaque body, hard-shell gelatin capsule filled with white to off-white beads. The capsule is axially printed with **MYLAN** over **OM 10** in black ink on both the cap and the body.

Q-OMEPRAZOLE 20 mg delayed release capsules, USP, are no. 2, red brown opaque cap / light pink opaque body, hard-shell gelatin capsule filled with white to off-white beads. The capsule is axially printed with **MYLAN** over **OM 20** in black ink on both the cap and the body.

The 10 mg delayed-release capsules are provided in HDPE bottles of 30 and the 20 mg delayed-release capsules are provided in HDPE bottles of 30, 100 and 500.

INFORMATION FOR THE CONSUMER

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

Pr Q-OMEPRAZOLE

(omeprazole delayed release capsules, USP)

Read this leaflet carefully. It contains general points about Q-OMEPRAZOLE and should add to more specific advice from your doctor or pharmacist.

WHAT IS Q-OMEPRAZOLE USED FOR AND HOW DOES IT WORK?

Q-OMEPRAZOLE contains the drug omeprazole.

The most common uses of Q-OMEPRAZOLE are:

- for stomach ulcers or for duodenal ulcers, including ulcers caused by infection with a bacterium called *Helicobacter pylori*;
- for ulcers caused by your medicine for pain and joint problems (NSAID-associated gastric and duodenal ulcers);
- for reflux esophagitis (tissue damage caused by stomach contents flowing back up the food pipe);
- and for symptoms of reflux disease such as heartburn and regurgitation.

Q-OMEPRAZOLE may also be used in rare conditions like "Zollinger-Ellison syndrome," where the stomach produces large amounts of acid. Q-OMEPRAZOLE works by reducing the amount of acid made in your stomach. This helps in treating acid-related and bacteria-related stomach problems.

Your doctor will have explained why you are being treated with Q-OMEPRAZOLE and will have told you what dose to take. Follow those directions carefully. They may differ from the information contained in this leaflet.

WHAT IS IN Q-OMEPRAZOLE?

Each Q-OMEPRAZOLE capsule contains omeprazole as the active ingredient. In addition, it contains the following non-medicinal ingredients (listed in alphabetical order): ammonium hydroxide, dibutyl sebacate, ethyl cellulose, fumed silica, hydroxypropylmethyl cellulose, methacrylic acid copolymer dispersion, oleic acid, sugar spheres, talc, titanium dioxide, and triethyl citrate. Both 10 mg and 20 mg capsule shells contain FDA/E172 red iron oxide, titanium dioxide and gelatine.

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

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING Q-OMEPRAZOLE?

Tell your doctor

- about **all** health problems you have now or have had in the past;
- about severe liver problems you have now or have had in the past;
- about other medicines you take, including ones you can buy without a prescription. Drug effects may be influenced if Q-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), and St. John's Wort (*Hypericum performatum*); or a certain type of anticancer drug (erlotinib or any other anticancer drug from the same class);
- if you are taking medication for HIV. Q-OMEPRAZOLE may decrease the effectiveness of some drugs used for HIV treatment; atazanavir and nelfinavir should not be used with Q-OMEPRAZOLE;
- if you are taking a high-dose of methotrexate (a drug used in high doses to treat cancer).Q-OMEPRAZOLE may need to be temporarily withdrawn;
- if you are taking clopidogrel, which is used for the prevention of blood clots. Q-OMEPRAZOLE may interact with this drug, therefore use with clopidogrel should be avoided;
- if you are pregnant, plan to become pregnant or are breastfeeding.

* not marketed in Canada

WHEN SHOULD Q-OMEPRAZOLE NOT BE USED?

If you are allergic to omeprazole or any of the other ingredients in Q-OMEPRAZOLE (see "What is in Q-OMEPRAZOLE?").

HOW DO I TAKE Q-OMEPRAZOLE PROPERLY?

Take all doses of Q-OMEPRAZOLE, as recommended by your doctor, even when you feel well. Daily doses are needed to help damaged areas heal. In general, the recommended dose for treating acute disease is 10-40 mg once a day for 2-8 weeks. Your doctor may recommend that you continue taking Q-OMEPRAZOLE 10-40 mg to control symptoms of reflux disease or to prevent reflux esophagitis from coming back, or Q-OMEPRAZOLE 20 mg to prevent ulcers from returning while you continue to take your medicine for pain and joint problems.

Take Q-OMEPRAZOLE until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if Q-OMEPRAZOLE is stopped too soon. Q-OMEPRAZOLE needs to be taken for the full duration of treatment to help correct acid problems.

If you miss a dose of Q-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 capsule. Do not double the dose. Just take your next dose on time.

Q-OMEPRAZOLE may be taken with food or on an empty stomach.

DO NOT OPEN, DIVIDE, CRUSH, OR CHEW THE CAPSULE

ARE THERE ANY SIDE EFFECTS?

Like any medication, Q-OMEPRAZOLE may cause side effects in some people. Side effects that do occur are usually mild and go away a short time after starting Q-OMEPRAZOLE.

Talk with your doctor if you suffer from any of these effects or if you get any other unusual or unexpected symptoms. These side effects may not be caused by Q-OMEPRAZOLE in your case, but only a doctor can assess this.

Common side effects that may occur (frequency of greater than or equal to 1 in 100 patients):

- Headache, diarrhea, constipation, abdominal pain, nausea/ vomiting, and excess gas in stomach (flatulence).

Uncommon side effects that may occur (frequency of greater than or equal to 1 in 1000 patients, but less than 1 in 100 patients):

- Dizziness, sensation of movement of one's self or of one's surroundings (vertigo), difficulty sleeping, feeling sleepy, sensation of burning/ prickling/ numbness, skin reactions (such as skin rash, dermatitis, itchy skin and/or hives) and feeling ill.

Rare side effects that may occur (frequency of less than 1 in 1000 patients):

- Dry mouth, inflammation in the mouth, gastrointestinal fungal infection, kidney and liver problems (i.e., inflammation of the kidney, inflammation of the liver with or without jaundice, impaired liver function), blood disorders (reduced number of cells in the blood, low blood sodium), inflammation in the gut (leading to diarrhea), sore joints and muscles, muscular weakness, development of breasts in males, sensitivity to sunlight, severe skin reactions, hair loss, hypersensitive (allergic) reactions (such as swelling of tissues, fever, discomfort/ tightness in chest and anaphylactic shock), increased sweating, blurred vision, and taste disorders. If you already have severe liver disease, you may experience disorientation/ aggression/ confusion/ decreased consciousness. If you are very ill, you may feel confused, nervous, depressed or hallucinate.

Very rare side effects that may occur (frequency of less than 1 in 10000 patients) include low blood magnesium (which may result in low blood calcium).

Long-term use of proton pump inhibitors may lead to low blood magnesium in some people; and when blood magnesium is lower than normal it has been reported in the literature that this may also lead to low blood calcium and low blood potassium.

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 call your doctor or pharmacist immediately and stop taking the drug combination.

As with other proton pump inhibitors, stopping Q-OMEPRAZOLE therapy after taking it for a long time, may cause an increase in secretion of stomach acid and associated acid-related symptoms. Carefully follow your doctor's instructions when discontinuing your Q-OMEPRAZOLE therapy.

Talk to your health care provider about your risk of bone fracture if you are taking Q-OMEPRAZOLE for a long time. People who take multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist, or spine. You should take Q-OMEPRAZOLE exactly as prescribed by your doctor.

Long term use of proton pump inhibitors may prevent normal absorption of Vitamin B12 from the diet and could lead to Vitamin B12 deficiency. You should take Q-OMEPRAZOLE exactly as prescribed by your doctor.

Other unwanted effects, which cannot be predicted, may occur in rare cases. If you experience any bothersome or unusual effects while using Q-OMEPRAZOLE, check with your doctor or pharmacist right away.

WHAT SHOULD I DO IN CASE OF OVERDOSE?

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

No severe symptoms have been seen in patients who have taken doses up to 400 mg.

WHERE SHOULD I KEEP Q-OMEPRAZOLE?

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 Q-OMEPRAZOLE well out of reach of children. Keep the package at room temperature (15ºC to 25°C). Do not keep Q-OMEPRAZOLE in the bathroom medicine cabinet or other warm, moist places. Protect from light.

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

Important Note:

This leaflet alerts you to some of the times you should call your doctor. If you experience symptoms that may indicate a more serious stomach or intestinal problem, you should contact your doctor immediately. Such symptoms may include any of the following: difficulty swallowing, unintentional weight loss, vomiting blood or food, or black (blood-stained) stools. Other situations, which cannot be predicted, may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using Q-OMEPRAZOLE.

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, QD Pharmaceuticals ULC, at: 1-800-575-1379.

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

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-800-661-3429 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada,
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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.

CLINICAL TRIALS

Comparative Bioavailability Studies

Two bioequivalence studies were conducted comparing Q-OMEPRAZOLE DR capsules (omeprazole base delayed release capsules) with Losec® (omeprazole base) as follows:

1. A blinded, randomized, single-dose, two way crossover oral bioequivalence study of Q-OMEPRAZOLE (omeprazole base) delayed-release 20 mg capsules and Losec® (omeprazole base) delayed-release 20 mg capsules was conducted in thirty-one (31/32) normal, healthy male and female subjects (age range = 20 – 54) under fasting conditions.

2. A blinded, randomized, single-dose, two way crossover oral bioequivalence study of Q-OMEPRAZOLE (omeprazole base) delayed-release 20 mg capsules and Losec® (omeprazole base) delayed-release 20 mg capsules was conducted in sixty-nine (69/72) normal, healthy male and female subjects (age range = 18 – 55) under fed conditions.

The results of the fasting and fed bioequivalence studies are provided in the Tables 3 and 4.

Table 3 A summary of the comparative bioavailability data under fasting conditions

Omeprazole (1 x 20 mg) From measured data **Geometric Mean[+] Arithmetic Mean (CV %)**				
Parameter	**TEST[*]**	**REFERENCE[†]**	**% Ratio of Geometric Means[+]**	**90% Confidence Interval[+]**
AUC_T (ng·h/mL)	568.35 844.2 (104)	608.86 893.2 (104)	93.4	89.7 – 97.2
AUC_I (ng·h/mL)	575.47 851.7 (104)	615.30 945.2 (101)	93.5	89.6 – 97.6
C_{max} (ng/mL)	301.18 352.5 (57)	357.91 435.5 (64)	84.2	76.4 - 92.7
T_{max}[§] (h)	2.484 (47.2)	2.083 (58.4)		
$T_{½}$[§] (h)	1.025 (43.54)	0.989 (42.63)		

[*] Q-OMEPRAZOLE (omeprazole base) 20 mg delayed-release capsules (Manufactured by QD Pharmaceuticals ULC, Canada).

[†] Losec® (omeprazole base) 20 mg delayed-release capsules by AstraZeneca Canada Inc. were purchased in Canada.

[§] Expressed as the arithmetic mean (CV%) only.

Table 4 A summary of the comparative bioavailability data under fed conditions

Omeprazole (1 x 20 mg) From measured data Geometric Mean[±] Arithmetic Mean (CV %)				
Parameter	**TEST[*]**	**REFERENCE[†]**	**% Ratio of Geometric Means[+]**	**90% Confidence Interval[±]**
AUC_T (ng·h/mL)	324.08 455.4 (124)	352.09 466.6 (121)	92.0	85.8 – 98.8
AUC_I (ng·h/mL)	334.49 466.9 (128)	357.61 510.7 (122)	93.5	87.4 – 100.1
C_{max} (ng/mL)	102.23 133.8 (74.9)	118.15 140.3 (64.4)	86.5	76.0 – 98.5
T_{max}[§] (h)	7.095 (31.3)	6.254 (29.2)		
$T_{½}$[§] (h)	1.415 (73.3)	1.255 (60.3)		

[*] Q-OMEPRAZOLE (omeprazole base) 20 mg delayed-release capsules (Manufactured by QD Pharmaceuticals ULC, Canada).

[†] Losec® (omeprazole base) 20 mg delayed-release capsules by AstraZeneca Canada Inc. were purchased in Canada.

[§] Expressed as the arithmetic mean (CV%) only.

Q-OMEPRAZOLE DR 20 mg capsules and Losec® 20 mg capsules were found to be bioequivalent.

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 μmol/kg (given as enteric-coated granules) inhibited histamine-stimulated gastric acid secretion by about 20% when measured 24 hours after the first dose, and by 60-65% when measured 24 hours after dosing at steady state. Once steady-state conditions were reached (after 3-5 days), acid inhibition remained unchanged, as established in dogs treated for periods 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 3 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.

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 antisecretory 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 three 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.

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 drugdrug 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 i.v. 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 4 Acute toxicity studies of omeprazole

SPECIES	SEX	ROUTE	LD_{50} (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
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 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.

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, 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.

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

15. 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.

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

17. 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.

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

19. AstraZeneca Canada Inc. Product Monograph for Losec®, Date of revision: September 3, 2014; Submission Control Number 176545.