PRODUCT MONOGRAPH

OMEP

Omeprazole delayed release capsules
20 mg omeprazole

USP Standard

H+/K+-ATPase Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Delayed release capsule 20 mg omeprazole	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

OMEP (omeprazole) capsules indicated for the treatment of frequent heartburn. Frequent heartburn is heartburn that occurs 2 or more days a week.

OMEP capsules not indicated for infrequent heartburn (i.e. one episode of heartburn a week or less) or immediate relief of heartburn.

CONTRAINDICATIONS

- Hypersensitivity to omeprazole, substituted benzimidazoles or any of the components of this medication (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS

General

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

Concomitant administration with atazanavir and nelfinavir is not recommended (see DRUG INTERACTIONS).

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, 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 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 DRUG INTERACTIONS).

Patients should be advised to consult their doctor if:

- Their heartburn continues or worsens.
- They need to take omeprazole for more than 14 days or require more than 1 course of treatment within a 4-month period.
- They experience heartburn with lightheadedness, sweating or dizziness.
- They have chest pain or shoulder pain with shortness of breath, sweating, pain spreading to arms, neck or shoulders, or lightheadedness.
- They have frequent chest pain.
- They have frequent wheezing, particularly with heartburn.
- They have stomach pain.

Carcinogenesis and Mutagenesis
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 of high-dose treatment in mice (14 - 140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 7 years did not cause any carcinoids.

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

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

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

Gastrointestinal
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore,

it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

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

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

Decreased gastric acidity due to any means, including any PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella, Campylobacter* and possibly *Clostridium difficile*.

Special Populations

Pregnant Women: The safety of omeprazole in pregnancy has not been established. Omeprazole capsules should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Women: It is not known if omeprazole is secreted in human milk. Omeprazole capsules should not be given to nursing mothers unless its use is considered essential.

Pediatrics (<18 years of age): The safety and effectiveness of omeprazole capsules in children have not yet been established. Omeprazole capsules should not be used in children under 18 years of age.

Geriatrics (>65 years of age): Based on data obtained from studies with intravenous (i.v.) administration of omeprazole and oral administration of omeprazole capsules, elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination of half-life (to 1.0 hour). The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: Based on data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules, 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). A dose of 20 mg omeprazole capsules given once daily to these patients for 4 weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Renal Impairment: Based on data obtained from studies with i.v. administration of omeprazole

and oral administration of omeprazole capsules, 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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Omeprazole is well tolerated. Most adverse reactions have been mild and transient, and have shown no consistent relationship with treatment.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events have been recorded during 6 placebo-controlled clinical investigations of OTC omeprazole involving 6286 subjects who took omeprazole (3,146 on omeprazole 20 mg and 3139 on omeprazole 10 mg) and 3120 subjects who took placebo. The most commonly reported adverse events in the omeprazole 20 mg group were headache (3%), diarrhea (2%) and infection (2%). These incidences were not significantly greater than those observed in subjects treated with placebo.

Table 1. Most Common Adverse Events in OTC Subjects in Placebo-Controlled Studies

	Omeprazole 20 mg (N=3146)		**Placebo (N=3120)**	
	N	**%**	**N**	**%**
Overall	470	15%	442	14%
Headache	102	3%	109	3%
Diarrhea	54	2%	56	2%
Infection	51	2%	62	2%
Nausea	36	1%	30	1%
Pain Abdominal	35	1%	29	1%
Flatulence	22	1%	14	<1%
Pain Back	21	1%	16	1%
Vomiting	19	1%	18	1%
Pharyngitis	19	1%	12	<1%
Flu Syndrome	17	1%	13	<1%

	Omeprazole 20 mg (N=3146)		Placebo (N=3120)	
	N	%	N	%
Rhinitis	17	1%	14	<1%
Dyspepsia	16	1%	9	<1%
Pain	16	1%	10	<1%

The percentage of discontinuations due to adverse events was also similar for omeprazole-treated subjects (0.5%) compared to placebo-treated subjects (0.6%), and were primarily due to nausea, headache, vomiting, diarrhea and/or abdominal pain.

The incidence of serious adverse events (SAEs) was low: 0.2% for omeprazole 20 mg subjects and 0.1% for placebo subjects. No SAE reported by subjects receiving omeprazole 20 mg was considered to be possibly or probably related to study medication.

The following is a list of adverse events reported in clinical trials or reported from routine postmarketing surveillance of short term and chronic use of omeprazole. 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.

Blood and Lymphatic System: Rare: leukopenia, thrombocytopenia, agranulocytosis and pancytopenia. Very rare: aplastic anemia and bone marrow suppression.

Cardiac: Very rare: serious arrhythmia (increased QT interval, torsade de pointes, ventricular fibrillation, ventricular tachycardia).

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

Ear and Labyrinth: Very rare: tinnitus, vertigo, hearing loss and ear pain.

Endocrine: Rare: gynaecomastia.

Eye: Very rare: eye pain, papilledema, optic atrophy.

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

Hepatobiliary: Uncommon: increased liver enzyme levels. Rare: encephalopathy in patients with pre-existing severe liver disease, hepatocellular necrosis requiring liver transplantation, hepatitis with or without jaundice and hepatic failure.

Musculoskeletal and Connective Tissue: Rare: arthralgia, muscular weakness and myalgia.

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): Very rare: gastric polyps, gastric cancer and gastric carcinoids.

Renal and Urinary: Rare: glycosuria, haematuria and pyuria.

Reproductive System and Breast: Very rare: impotence, decreased fertility.

Skin and Subcutaneous Tissue: 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 and interstitial nephritis and anaphylactic shock; increased sweating, peripheral edema, blurred vision, taste disturbances and hyponatremia.

DRUG INTERACTIONS

The gastric acid suppression during treatment with omeprazole and other PPIs 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 P450 system (CYP), mainly in the liver. The pharmacokinetics of the following drugs, which are also metabolized through the cytochrome P450 system, have been evaluated during concomitant use of omeprazole capsules in humans: aminopyrine, antipyrine, clopidogrel, diazepam, phenytoin, warfarin (or other vitamin K antagonists), cilostazol*, theophylline, voriconazole, digoxin, propranolol, metoprolol, lidocaine, quinidine, ethanol, piroxicam, diclofenac and naproxen.

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 clarithromycin 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.

As omeprazole is metabolized through CYP 2C19, it can alter the metabolism and prolong elimination of diazepam, warfarin (R-warfarin), phenytoin, and cilostazol*.

*not marketed in Canada

There is a modest increase in the absorption of digoxin when omeprazole is co-administered in daily doses of 20 mg or 40 mg. This increase may be clinically relevant in patients who have renal impairment or are especially susceptible to digoxin toxicity.

Drug-Drug Interactions

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

Aminopyrine and Antipyrine
After 14 days of 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 of administration of 30 mg once daily, no significant changes in clearance were noted.

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

Antibiotics
Clarithromycin
Clarithromycin is known to inhibit CYP 2C19 and CYP 3A4, which may lead to increased omeprazole serum levels by decreasing the rate of omeprazole's metabolism.

Erythromycin
In vivo data suggests that omeprazole does not inhibit the metabolism of erythromycin; however, as erythromycin is an inhibitor of CYP3A4, there is a potential for an interaction in which metabolism of omeprazole is decreased, which may lead to an increase in serum levels of omeprazole.

Antifungal Drugs
Itraconazole and Ketoconazole
The absorption of some drugs might be altered due to the decreased intragastric acidity. Thus, it can be predicted that the absorption of itraconazole and ketoconazole will decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

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.

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} by more than 70%. 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 (see WARNINGS AND PRECAUTIONS). 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.

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

*not marketed in Canada

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, 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%. 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 acetyl salicylic acid (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 cardiovascular 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 clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA (see WARNINGS AND PRECAUTIONS).

Diazepam
As omeprazole is metabolized through CYP 2C19, it can alter the metabolism and prolong elimination of 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%.

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 10 healthy subjects increased the bioavailability of digoxin by an average of 10% (up to 30% in 2 out of 10 subjects).

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

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

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 AND PRECAUTIONS).

NSAIDs (e.g., Piroxicam, Diclofenac and Naproxen)
There were no significant effects on the steady state pharmacokinetics of piroxicam, diclofenac, and naproxen following repeated dosing with omeprazole 20 mg in healthy volunteers.

Phenytoin
As omeprazole is metabolized through CYP 2C19, it can alter the metabolism and prolong elimination of phenytoin. Following three weeks of 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 i.v. and oral doses of omeprazole capsules 40 mg in young, healthy volunteers, the clearance of phenytoin was decreased by 15-20%, and half-life was prolonged by 20-30%. Following repeated dosing with omeprazole 40 mg once daily, the elimination half-life of phenytoin was increased by 27%. Thus, there appears to be a dose-dependent inhibition of elimination of phenytoin by omeprazole.

Patients receiving phenytoin should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

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.

Quinidine

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

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.

Warfarin (or other Vitamin K antagonists)
As omeprazole is metabolized through CYP 2C19, it can alter the metabolism and prolong elimination of warfarin (R-warfarin). 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.

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.

Drug-Food Interactions
No interaction with food has been found.

Drug-Herb Interactions
Drugs known to induce CYP 2C19 or CYP 3A4 or both, such as St John's Wort (*Hypericum performatum*) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

Drug-Laboratory Interactions
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 PPI treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalized by this time.

DOSAGE AND ADMINISTRATION

The recommended dose of OMEP (omeprazole) for **adults 18 years and older** is 1 capsule given once daily for 14 days for the treatment of frequent heartburn (i.e. for heartburn that occurs more

than 2 days a week). The maximum dose is 1 capsule in a 24-hour period. Symptom relief should be rapid. If symptom control is not achieved after 2 weeks, further investigation is recommended.

The capsules should be swallowed whole with sufficient water. A 14-day course of therapy may be repeated every 4 months.

Patients with Renal Impairment: No dose adjustment is required (see WARNINGS AND PRECAUTIONS).

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

Geriatrics (>65 years of age): No dose adjustment is required. The daily dose should not exceed 20 mg (see WARNINGS AND PRECAUTIONS).

Missed Dose

A missed dose may be taken within 12 hours of the scheduled time. If more than 12 hours have passed since the scheduled time, the missed dose should be skipped.

OVERDOSAGE

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 capsules 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 4,000 mg/kg. In dogs, the only sign of acute toxicity was vomiting, which occurred at doses of approximately 600 mg/kg (see TOXICOLOGY).

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Omeprazole inhibits the gastric enzyme H^+/K^+-ATPase (the proton pump) which catalyzes the exchange of H+ and K+. Omeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose-dependent. Daily oral doses of omeprazole 20 mg and higher showed a consistent and effective acid control.

Pharmacodynamics

Information from clinical trials in patients with duodenal ulcers in remission indicate that omeprazole demonstrate the inhibition of stimulated acid secretion and a mean reduction of 24-hour intragastric pH of approximately 80% was achieved during repeated dosing of 20 mg daily

Pharmacokinetics

Summary of Omeprazole Pharmacokinetic Parameters in Healthy Male Volunteers

Single Dose Arithemetic Mean	Cmax (ng/mL)	Tmax[§] (h)	$t_{1/2}$ (h)	AUC_I (ng• h/mL)
Fasted	310.50	2.85	0.97	569.48
Fed	371.73	7.50	0.85	623.48

[§] Expressed as the median

Absorption: Omeprazole is absorbed rapidly. Food has no effect on the bioavailability of the capsule. Peak plasma levels occur within about four hours.

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.

Metabolism and Excretion: 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 PPIs, exhibits polymorphism. Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP 2C19 enzyme and are called poor metabolisers.

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

Special Populations and Conditions

Geriatrics: Elderly subjects showed a 36% increase in bioavailability, reduced total plasma clearance and reduced urinary excretion of metabolites. Elimination half-life was also prolonged by 50%. The mean urinary excretion of metabolites was 68% of the dose. These changes are consistent with reduction in pre-systemic and systemic elimination, typical in the elderly. The daily dose should, as a rule, not exceed 20 mg in this patient group (see WARNINGS AND PRECAUTIONS).

Hepatic Impairment: Patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance, and a four-fold prolongation of the elimination half-life. Dosage for patients with liver cirrhosis and other liver dysfunction should, as a rule, not exceed 20 mg daily (see WARNINGS AND PRECAUTIONS).

Renal Impairment: The pharmacokinetics of omeprazole in patients with impaired renal function was virtually the same as in healthy subjects.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OMEP are hard gelatin capsules 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.

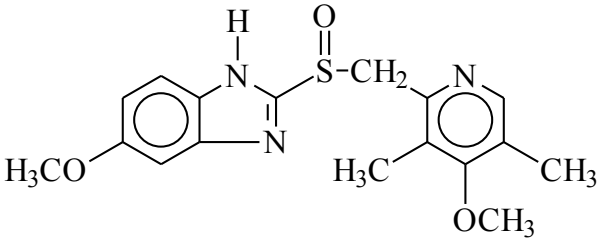
OMEP (omeprazole) delayed release capsules contain 20 mg/capsule of omeprazole.

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.

Available in blister packs of 14 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance	
Proper Name	Omeprazole
Chemical Name	5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl}-1H-benzimidazole.
Molecular Formula	$C_{17}H_{19}N_3O_3S$
Molecular Weight	345.4 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.

CLINICAL TRIALS

Heartburn

The prevention of frequent heartburn by omeprazole magnesium has been examined in two pivotal randomized, double-blind, placebo-controlled trials conducted in 2086 subjects with heartburn 2 or more days per week. With consecutive daily dosing for 14 days, omeprazole- treated subjects had a significantly greater percentage of heartburn free days than did placebo- treated patients (64.4% *vs.* 39.4%; $p<0.001$, Study 1 and 67.8% *vs.* 37.9%; $p<0.001$, Study 2). Omeprazole magnesium-treated subjects had a greater percentage of nights with no nocturnal heartburn symptoms (84.7% *vs.* 74.5%; $p\leq0.05$, Study 1 and 86.1% *vs.* 75.4%; $p\leq0.05$, Study 2). Consecutive daily dosing with omeprazole magnesium also resulted in a greater percentage of days with no more than mild heartburn *vs.* placebo. For all 14-day outcomes, omeprazole magnesium provided significantly greater protection against heartburn than placebo in both studies.

Comparative Bioavailability Studies

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

DETAILED PHARMACOLOGY

Animal Pharmacology

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

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

days), acid inhibition remained unchanged, as established in dogs treated for periods of up to one year.

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

Due to the potency and long duration of action of omeprazole, repeated administrations of high doses in the rat resulted in a marked decrease of acid secretion and a secondary hypergastrinemia and hyperplasia of G-cells. In rats, administration of omeprazole 14-140 mg/kg/day resulted in plasma gastrin levels of 1,000-3,000 pg/mL as compared to 150-200 pg/mL in controls. In dogs, high doses of omeprazole (28 mg/kg/day) produced marked hypergastrinemia (1,000-2,000 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 or on exploratory activity was recorded, suggesting that omeprazole is devoid of sedative or neuroleptic effects.

Other Interactions

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

Pharmacokinetics

Absorption and Distribution

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

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

Metabolism and Excretion

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

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

Human Pharmacology

Pharmacodynamics

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

Table 2. Percentage Inhibition of Mean Acid Output After Single Oral Doses of Omeprazole

Stimulus	Type of Subjects	Omeprazole Dose (mg)		Time After Dose (h)
		20	80	
Basal	Hsu*	33%		1-4
Basal-Nocturnal	DU (rem)**	49%		15-24
Sham Feeding	HSu	23%		1.5-3.5
Betazol	HSu	38%		1-4
Pentagastrin	HSu	36%		1-4
Basal	ZES***		97%	2-3
* Healthy subject, **Duodenal ulcer in remission, ***Zollinger-Ellison syndrome				

Repeated 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 (data taken from clinical studies using omeprazole capsules). **No clinically significant effects** attributable to the drug could be found for the following parameters: *Endocrine:* plasma levels of insulin, C- peptide, glucagon, parathyroid hormone, 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 central nervous system 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-dependant 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

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	M	p.o.[1*]	>4,000
	F	p.o.[1*]	>4,000
Mouse	M	p.o.[1]	1,520
	F	p.o.[1]	1,380
Mouse	M	i.v.	83
	F	i.v.	>100
Rat	M	p.o.[1*]	>4,000
	F	p.o.[1*]	>4,000
Rat	M	p.o.[1]	>5,010
	F	p.o.[1]	3,320
Rat	M	i.v.	>40
	F	i.v.	>40

[1] Suspension in Methocel®, not buffered * Non-micronized test compound

The highest oral dose (4,000 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 LD50 was approximately 1,500 mg/kg in mice; in male rats, higher than the maximum dose (5,000 mg/kg); and in female rats, approximately 3000 mg/kg. As much as 80% of the compound may not have been absorbed due to acid degradation of these single doses in the stomach. Death occurred within 2 days of ingestion and was preceded by reduced motor activity, reduced respiration frequency but increased respiration depth, reduced body temperature, and twitching, tremor or convulsions. The highest oral dose given to dogs (660 mg/kg) caused vomiting within 40-100 minutes of ingestion. The acute i.v. LD50 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 H2-receptor blocker caused hypergastrinemia and increased ECL-cell density. In antrectomized rats given a high dose of omeprazole, plasma gastrin levels remained normal, and consequently there was no increase in ECL-cell density. It has therefore been concluded that (i) inhibition of gastric acid secretion by large doses of omeprazole or a histamine H2-receptor blocker, evokes a natural feedback response leading to hypergastrinemia, (ii) long-standing hypergastrinemia leads to gastric ECL-cell proliferation, and (iii) there is no direct trophic effect of omeprazole on gastric ECL-cells.

An additional long-term (24 months) toxicity study in female rats (1.8-14 mg/kg/day) confirmed that the ECL-cell carcinoids were extreme end-life tumours and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8-140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found and the ECL-cell hyperplasia recovered to normal during the next 12 months of no treatment.

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

Investigation in man has demonstrated an initial moderate increase in gastrin levels during treatment with omeprazole, but no further increase occurred during long-term (up to 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 pre-treatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

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PART III: CONSUMER INFORMATION

OMEP
Omeprazole delayed release capsules 20 mg

This leaflet is part III of a three-part "Product Monograph" published when OMEP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OMEP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
OMEP is recommended for Adults (18 years and older) to relieve **frequent heartburn** – when you have heartburn 2 or more days a week.

Heartburn is a painful burning feeling in the chest which rises up to the throat.

OMEP is not the right medicine for you if you suffer from heartburn once a week or less, or if you want immediate relief.

What it does:
OMEP belongs to a group of medicines called proton pump inhibitors which work by reducing the amount of acid the stomach makes.

OMEP works differently from other non-prescription heartburn products, such as antacids and other acid reducers. OMEP stops acid production at the source, the acid pump inside your stomach that produces acid.

Although OMEP will start to suppress acid within a few hours, it is not intended to give instant relief. You may have to wait 3 to 5 days to feel the full effect of the product on heartburn symptoms, although some people get complete relief of symptoms within 24 hours. Make sure you take the capsules for all 14 days even if you start to feel better.

What else can you do to help avoid your symptoms?

- Avoid or limit foods such as: caffeine, chocolate, spicy or fatty foods, and alcohol.
- Eat smaller, more frequent meals. Avoid eating or drinking late at night or 2-3 hours before bedtime.
- Avoid lying down or bending over soon after eating.
- Try to reduce stress.
- If you are overweight, try to reduce excess weight.
- If you smoke, try to stop smoking or reduce the amount you smoke.

When it should NOT be used:

You should not take OMEP if you think you might be allergic to omeprazole or any of the ingredients (see "What the non-medicinal ingredients are").

What the medicinal ingredient is:
The medicinal ingredient is omeprazole.

What the non-medicinal ingredients are:
Each 20 mg capsule contains the 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.

What dosage forms it comes in:
OMEP is available in capsules containing 20 mg of omeprazole.

WARNINGS AND PRECAUTIONS

Warnings. Do not use if:

- You have trouble or pain swallowing food, have bloody black stools or are vomiting with blood.
- You have been having frequent heartburn for over 3 months.

These may be signs of a more serious condition. You may need different treatment. See your doctor immediately.

OMEP may decrease the efficacy of some drugs used for HIV treatment (**atazanavir and nelfinavir**) or heart disease (**clopidogrel**); these drugs should not be used with OMEP.

BEFORE you use OMEP, talk to your doctor or pharmacist if you:

- are taking any other medicines to reduce stomach acid
- have heartburn with light-headedness, sweating or dizziness
- have chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders
- have frequent wheezing, particularly with heartburn
- have unexplained weight loss
- have nausea or vomiting
- have stomach pain
- have jaundice or other liver problems
- now have or in the past have had a gastric ulcer or surgery on your stomach or bowels
- **are pregnant, plan to become pregnant, or are breastfeeding**

STOP USE and ask your doctor if:

- you have severe and/or persistent diarrhea
- your heartburn continues or worsens
- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment within a 4-month period

INTERACTION WITH THIS MEDICATION

Drugs that may interact with OMEP include the following. Ask your doctor or pharmacist before use if you are taking:

- Atazanavir, Nelfinavir (medicines for HIV infection)
- Cilostazol* (a medicine to treat leg pain)
- Clarithromycin, Erythromycin (antibiotics)
- Clopidogrel (a heart medicine)
- Diazepam (an anxiety medicine)
- Digoxin (a heart medicine)
- Erlotinib (a medicine against cancer) or any other anticancer drug from the same class
- Ketoconazole, Itraconazole, Voriconazole (antifungal or anti-yeast medicines)
- Methotrexate (a medicine used against cancer)
- Phenytoin (an epilepsy medicine)
- St John's Wort (*Hypericum perforatum*)
- Tacrolimus (an immune system medicine)
- Warfarin (a blood-thinning medicine)

**not marketed in Canada*

PROPER USE OF THIS MEDICATION

Usual dose: Adults (18 years of age and older)

14-Day Course of Treatment

- Take 1 capsule with a glass of water, before eating in the morning.
- Do NOT chew or crush capsules. This decreases how well OMEP works.
- Do NOT take more than 1 capsule every 24 hours.
- Take every day for 14 days.
- Do NOT use for more than 14 days unless directed by your doctor.
- Do NOT repeat a 14-day course of treatment within a period of 4 months unless directed by your doctor.

When to Take OMEP Again:

You should wait at least 4 months before taking another 14-day course of treatment.

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.

Missed Dose:

If you miss a dose of OMEP 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. Just take your next dose on time.

SIDE EFFECT AND WHAT TO DO ABOUT THEM

OMEP may cause side effects in some people. Side effects are usually mild and go away a short time after starting OMEP. Common side effects that may occur: cold or flu-like symptoms, diarrhea, excess gas, headache, nausea or vomiting, stomach pain.

Uncommon side effects that may occur: altered liver values, dizziness, feeling of burning/prickliness/numbness of the skin, feeling sleepy, insomnia, itching, skin rash.

Other unwanted effects may occur in rare cases. If you experience any bothersome or unusual effects while using OMEP, check with your doctor or pharmacist right away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk with your doctor or pharmacist in all cases**	**Stop taking drug and call your doctor or pharmacist**
Rare (frequency of greater than or equal to 1 in 10,000 but less than 1 in 1,000 patients)		
Blurred vision		**x**
Confusion	**x**	
Depression	**x**	
Development of breasts in men	**x**	
Hallucinations	**x**	
Impaired liver function (skin and eyes appear yellow)		**x**
Inflammation in the mouth	**x**	
Muscle pain	**x**	
Muscle weakness	**x**	
Restlessness	**x**	
Severe allergic reaction (such as swelling or anaphylactic reaction/shock)		**x**
Severe skin reaction (rash with swelling, blisters and peeling of the skin, ulcers, often with high fever)		**x**
Sore joints	**x**	
Very Rare (frequency of less than 1 in 10,000 patients)		
Ear problems (pain, hearing loss, ringing sounds)		**x**
Eye problems (edema, pain)		**x**
Impotence	**x**	
Vertigo	**x**	

This is not a complete list of side effects. For any unexpected effects while taking OMEP contact your doctor or pharmacist.

HOW TO STORE IT

OMEP (omeprazole) 20 mg capsules are two-piece hard gelatin capsules with a dark pink cap, pink body, each imprinted with "OME 20".

Store blister packs at room temperature 15 - 30ºC. Protect from moisture.
Keep OMEP out of reach of children.
Do not keep OMEP in the bathroom medicine cabinet or other warm, moist places.
Do not use OMEP after the expiry date marked on the pack.

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;
- By calling 1-866-234-2345 (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.

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.

MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062
Or
by written request at:

145, Jules-Léger
Boucherville, (Québec), Canada
J4B 7K8

Or by e-mail at:
medinfo@sandoz.com

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