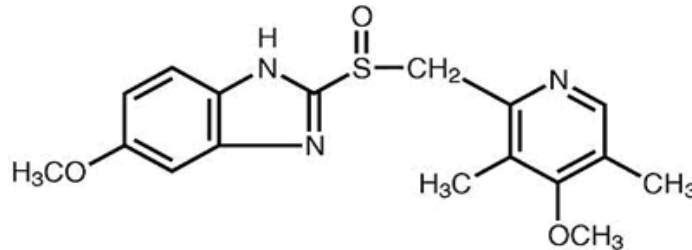


CHEMMART OMEPRAZOLE ENTERIC COATED TABLETS**NAME OF THE MEDICINE**

Omeprazole.

Chemical Name: 5-methoxy-2-[(*RS*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-sulphinyl]-1*H*-benzimidazole.

Structural Formula:



Empirical Formula: C₁₇H₁₉N₃O₃S

Molecular Weight: 345.4

CAS Number: 73590-58-6

DESCRIPTION

Omeprazole is a white or almost white powder, very slightly soluble in water, soluble in methylene chloride, sparingly soluble in alcohol and in methanol. It dissolves in dilute solutions of alkali hydroxides.

Each enteric coated tablet contains 20 mg omeprazole. It also contains ascorbyl palmitate, microcrystalline cellulose, crospovidone, magnesium stearate, povidone, lactose, purified talc, hypromellose phthalate, glycerol triacetate, iron oxide red, iron oxide black.

PHARMACOLOGY

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase, the proton pump, in the acid environment of the intracellular canaliculi within the parietal cell. This effect of omeprazole on the final step of the gastric acid formation process is dose dependent and effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production.

Omeprazole has no effect on acetylcholine or histamine receptors. No clinically significant pharmacodynamic effects, other than those explained by the effect on acid secretion, have been observed.

Effect on Gastric Acid Secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within 1 hour and is maximal within 2 hours. With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment.

A mean decrease of approximately 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients treated with an oral dose of omeprazole 20 mg. Omeprazole produces a mean decrease in peak pentagastrin stimulated acid output of approximately 70% 24 hours after dosing. When the drug is discontinued, secretory activities return to approximately 50% of maximum after 24 hours and gradually return to normal over 3–5 days.

Peptic Ulcer Disease Associated with *Helicobacter pylori*

Helicobacter pylori (*H. pylori*) is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. *H. pylori* is the major factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *H. pylori* and gastric carcinoma. An attempt to eradicate *H. pylori* is appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by non-steroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

In vitro testing has shown that omeprazole has an MIC₉₀ (minimum inhibitory concentration) of 25 µg/mL against *H. pylori*. However, *in vivo* it only suppresses the organism without eradicating it. The combination of omeprazole and antimicrobial agents results in eradication of the organism *in vivo*, despite the fact that antimicrobial agents administered singly have also proved ineffective in eradicating *H. pylori*. The mechanism of the synergy between omeprazole and antimicrobial agents in eradicating *H. pylori* is not completely understood. Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.

Eradication of *H. pylori* is associated with reduced peptic ulcer recurrence.

Other Effects Related to Acid Inhibition

During long term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are benign and appear to be reversible.

In some patients, fasting serum gastrin levels have been noted to rise 2- to 4-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

PharmacokineticsAbsorption

Omeprazole is acid labile and is administered orally as enteric coated tablets. Omeprazole is not released until the enteric coated tablet is dissolved in the duodenum.

Absorption is rapid with peak plasma levels of omeprazole occurring within 4 hours and is usually complete within 3–6 hours. The systemic bioavailability of omeprazole from a single oral dose of omeprazole enteric coated tablets is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on oral bioavailability, but may reduce the rate of absorption of omeprazole.

Distribution

The plasma protein binding of omeprazole is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration time curve (AUC), but not to the actual plasma concentration at any given time.

Metabolism

Omeprazole is entirely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphic CYP2C19. This CYP is responsible for the formation of hydroxyomeprazole, one of the major metabolites in plasma, and to a lesser extent, for the formation of 5-O-desmethyl omeprazole. The remaining part is mainly dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone.

Identified metabolites in plasma are the sulfone, the sulfide and hydroxyomeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration time curve following intravenous administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3–0.6 L/minute. There is no change in half-life during repeated dosage.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 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 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 CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxyomeprazole and the corresponding carboxylic acid.

CLINICAL TRIALS

1. Gastroesophageal Reflux Disease (GORD)

Symptomatic GORD

Randomised, controlled clinical trials (n = 1,710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after 4 weeks treatment comparing omeprazole 10 mg and 20 mg once daily with control groups of ranitidine 150 mg twice daily or placebo. The percentage of patients with complete relief of heartburn after 4 weeks is presented in Table 1.

Table 1: Percentage of Patients with Complete Relief of Heartburn at 4 Weeks

STUDY	GROUP (n)	RELIEF (% patients)	GROUP DIFFERENCE		
				%	95% CI
Lind	Placebo (105)	13	Omeprazole 10 – Placebo	18	9, 27
	Omeprazole 10 (199)	31	Omeprazole 20 – Placebo	33	23, 43
	Omeprazole 20 (205)	46	Omeprazole 20 – Omeprazole 10	15	6, 25
Venables	Ranitidine (135)	36	Omeprazole 10 – Ranitidine	0.2	-12, 12
	Omeprazole 10 (126)	36	Omeprazole 20 – Ranitidine	3.7	-8, 15
	Omeprazole 20 (130)	39	Omeprazole 20 – Omeprazole 10	3.5	-8, 15
Bate	Placebo (58)	22	Omeprazole 20 – Placebo	36	17, 55
	Omeprazole 20 (48)	58			

2. Erosive Oesophagitis

At the time of registration, seven randomised controlled clinical trials (n = 1,674) were evaluated to assess the efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis. Omeprazole 10 mg and 20 mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150 mg twice daily or placebo at 6 months. The difference in remission rates between omeprazole 10 mg and 20 mg favoured 20 mg. Three studies recorded remission rates over 12 months and an additional study continued for 18 months.

In a meta-analysis of five of the clinical trials (n = 1,154), 72% and 82% of patients remained in remission at 6 months on omeprazole 10 mg and 20 mg once daily, respectively. In a separate large study (n = 327), the remission rate following omeprazole 10 mg once daily for 18 months was 60%.

In two of the studies, patients who relapsed in the first 3 months of maintenance treatment were then healed and treated with a maintenance dose of omeprazole 20 mg. The difference in the total remission rate over 6 or 12 months, while small, suggests that it may be more difficult, or take longer, to obtain subsequent healing and control if 10 mg rather than 20 mg had been used for initial maintenance therapy.

Gastric safety data are available from seven controlled clinical trials of up to 2 years duration (irrespective of indication). A full analysis of these trials was undertaken as a consequence of histological changes observed in animals (see **PRECAUTIONS**). This involved a total of 1,128 patients with an evaluable series of biopsies; 843 patients treated continuously with omeprazole for 6–12 months, 77 patients completing 18 months, and 208 patients completing 2 years of continuous omeprazole treatment.

Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for 4 years, and in this continuing study, biopsies are available for at least 14 patients treated for up to 8 years. No instances of dysplasia or carcinoids of the gastric ECL cells have been reported in these studies. An association between focal hyperplasia and chronic gastritis with atrophy was found during long-term therapy. However, this finding is also observed in patients with untreated gastric ulcer disease with normal gastrin levels and is thus not a treatment related effect.

INDICATIONS

Gastroesophageal Reflux Disease (GORD)

- Symptomatic GORD
The relief of heartburn and other symptoms associated with GORD.
- Erosive Oesophagitis
The treatment and prevention of relapse.

Peptic Ulcers

- The treatment of duodenal and gastric ulcer.
- Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
- The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
- The prevention of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs in patients assessed as being at high risk of gastroduodenal ulcer or complications of gastroduodenal ulcer.
- Long-term prevention of relapse in gastric and duodenal ulceration, in patients proven to be *Helicobacter pylori* negative, or in whom eradication is inappropriate, e.g. the elderly or ineffective.

Zollinger-Ellison Syndrome

The treatment of Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole, substituted benzimidazoles or any other ingredient.

Omeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking proton pump inhibitors (PPIs) including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue omeprazole if acute interstitial nephritis develops.

Antimicrobial Resistance

The development of antimicrobial resistance may have an adverse effect on eradication regimens. The clinical impact of this resistance on *H. pylori* has not been comprehensively studied.

Concomitant Therapy with 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

p.o. 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 **INTERACTIONS WITH OTHER MEDICINES**).

Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with acid-suppressing medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria.

Effects of Acid Inhibition

Decreased gastric acidity due to any means including proton pump inhibitors increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Hepatic Insufficiency

Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a 4-fold prolongation of the elimination half-life. However, urinary recovery over 96 hours remains unchanged, indicating no accumulation of omeprazole or its metabolites. The normal dose of omeprazole 20 mg daily may be used in patients with severe liver disease (see **DOSAGE AND ADMINISTRATION**).

Osteoporotic Fractures

Some published case-controlled and observational studies suggest that proton-pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures.

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 developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Special Patient Populations – CYP2C19 enzyme

Approximately 3% of the Caucasian population and 15–20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of omeprazole is most likely catalysed by CYP3A4. 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 CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also 3 to 5 times higher. The implications of these findings need to be addressed from clinical perspective.

Undiagnosed Malignancy

As with all anti-secretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurring vomiting, dysphagia, hematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Effects on Fertility

There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at 7-fold clinical exposure was associated with embryofetal toxicity.

Use in Pregnancy (Category B3)

Results from three prospective epidemiological studies indicate that whilst there was no increase in the overall malformation rates compared with controls, the data indicated a potentially higher rate of cardiac defects in the omeprazole group.

There was no evidence of teratogenicity following administration of omeprazole to pregnant rats and rabbits during the period of organogenesis. Doses in rats were associated with systemic exposures of up to 16- and 14-fold (oral and intravenous administration, respectively) the anticipated exposure at the clinical dose of 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicity apart from increased locomotor activity in prenatally exposed offspring at systemic exposures approximating clinical exposure, based on plasma AUC.

In rabbits, oral doses were associated with systemic exposure less than clinical exposure (plasma AUC) and intravenous doses were up to 13-fold the 40 mg/day clinical dose (on a mg/m² basis). Embryofoetal toxicity and maternotoxicity occurred at doses associated with less than clinical exposures.

Use in Lactation

Omeprazole and its metabolites are excreted in milk in rats but it is not known if this occurs in humans. In rats, reduced offspring postpartum growth rate was observed following administration of omeprazole during late gestation and throughout lactation at oral doses of 138 mg/kg/day and above (7-fold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure).

It is recommended that omeprazole not be used in breastfeeding mothers.

Genotoxicity

Omeprazole has been subjected to a battery of *in vitro* and *in vivo* genotoxicity tests to examine the mutagenic, clastogenic and DNA damaging potential of the drug. The *in vitro* assays include the Ames test, mouse lymphoma TK locus forward mutation assay and a chromosome aberration test in human lymphocytes. The *in vivo* tests were a chromosome aberration test in mouse bone marrow, an alkaline elution/rat liver DNA damage assay and two mouse micronucleus tests.

No evidence of significant genotoxicity was seen in these tests.

Carcinogenicity

In a two-year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner, in both male and female rats. The incidence of these effects was markedly higher in female rats.

The same effects were seen in an additional two-year study in female rats at daily doses of 1.7, 3.4 and 13.8 mg/kg/day. A no-effect dose was not established in female rats in the dose ranges studied.

In mice, a 78-week carcinogenicity study was performed according to relevant regulatory and scientific standards. No gastric ECL cell carcinoids were seen. However, longer term studies have not been performed in this species.

Hypergastrinaemia, ECL cell hyperplasia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole. These include the following:

- a. Exogenous Gastrin Infusion
Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL cells following treatment for 1 month.
- b. H₂-receptor Antagonists
In rats administered ranitidine 2 g/kg/day in their diet over 106 weeks, argyrophilic cell hyperplasia was observed in 37% of the animals and gastric carcinoids were found in 19% of the treated group.
- c. Surgical Resection of the Acid Producing Oxyntic Mucosa
In rats in whom 75% of the stomach corpus was surgically removed, 26 of 75 animals developed ECL cell carcinoids during the 124-week study.

These findings show that the development of ECL cell carcinoids in the rat is directly related to hypergastrinaemia rather than a direct effect of omeprazole on the ECL cell.

Omeprazole may also affect other cells in the gastrointestinal tract (e.g. G cells) either directly or by inducing sustained hypochlorhydria, but this possibility has not been extensively studied.

Effect on Ability to Drive or Operate Machinery

No effects have been observed.

INTERACTIONS WITH OTHER MEDICINES

Absorption

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

Omeprazole produces a profound and sustained inhibition of gastric acid secretion. The absorption of compounds whose absorption depends on gastric pH, e.g. ketoconazole, itraconazole, erlotinib etc, may decrease and the absorption of drugs such as digoxin can increase during treatment with omeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Co-administration of omeprazole in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving omeprazole and mycophenolate mofetil. Use omeprazole with caution in transplant patients receiving mycophenolate mofetil.

Metabolism

Cytochrome P450 Effects

Omeprazole is mainly metabolised *via* the hepatic cytochrome P450 system (CYP2C19) and may be expected to interact with the metabolism of other drugs metabolised by this enzyme.

Effects of Omeprazole on Other Drugs

Diazepam

Following dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54% and the mean elimination half-life of diazepam was increased by 130%, with a consequent significant increase in plasma diazepam concentrations. For omeprazole 20 mg, the clearance of diazepam was decreased by approximately 25% in the majority of the population, while no change was detected in poor metabolisers. Consideration should be given to a reduction in diazepam dosage when omeprazole enteric coated tablets are co-prescribed.

Phenytoin

Omeprazole 40 mg daily for seven days reduced plasma clearance of intravenous phenytoin by 15–20% and increased the elimination half-life by 27%. Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. In a study that administered omeprazole 20 mg to epileptic patients, steady-state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin

Concomitant administration of omeprazole 20 mg to patients on continuous treatment with warfarin caused a slight though statistically significant increase in the plasma concentration of the *R*-enantiomer of warfarin. Plasma concentrations of the more potent *S*-enantiomer were not affected and no change in warfarin's anticoagulant activity was observed.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol

Omeprazole 40 mg daily for 7 days increased C_{max} and AUC for cilostazol by 18% and 26%, respectively, and one of its active metabolites by 29% and 69%, respectively (see **CONTRAINDICATIONS**).

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is not recommended.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are *via* CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Clopidogrel

Studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic (PK/PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, *i.e.* four times the recommended dose), resulting in a decreased exposure of 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.

When clopidogrel was given together with a fixed-dose combination of esomeprazole 20 mg and aspirin 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 similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + aspirin) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Tacrolimus

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Potential Interactions that have been excluded

Results from a range of *in vivo* interaction studies with omeprazole versus other drugs indicate that omeprazole 20–40 mg, given repeatedly, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac, naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine, oestradiol).

Effects of Other Drugs on Omeprazole

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing the rate of metabolism of omeprazole.

Drugs known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin or voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of metabolism of omeprazole.

Clarithromycin

Plasma concentrations of omeprazole are increased during concomitant administration.

Voriconazole

Concomitant administration of omeprazole and the CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure.

Effects on Laboratory Tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the omeprazole treatment should be temporarily stopped five days before CgA measurements.

ADVERSE EFFECTS

Omeprazole enteric coated tablets are well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with treatment.

Adverse reactions within each body system are listed in descending order of frequency (very common: $\geq 10\%$; common: $\geq 1\%$ and $< 10\%$; uncommon: $\geq 0.1\%$ and $< 1\%$; rare: $\geq 0.01\%$ and $< 0.1\%$; very rare: $< 0.01\%$). These include the following:

Blood and lymphatic disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia.

Immune system disorders

Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders

Rare: Hyponatraemia.

Very rare: Weight increase, hypomagnesaemia and hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.

Psychiatric disorders

Uncommon: Insomnia.

Rare: Agitation, aggression, reversible mental confusion, depression, hallucinations.

Nervous system disorders

Common: Headache.

Uncommon: Dizziness, paraesthesia, somnolence.

Rare: Taste disturbance.

Eye disorders

Rare: Blurred vision.

Ear and Labyrinth disorders

Uncommon: Vertigo.

Respiratory thoracic and mediastinal disorders

Rare: Bronchospasm.

Very rare: Dyspnoea.

Gastrointestinal disorders

Common: Diarrhoea, constipation, abdominal pain, nausea/vomiting, flatulence.

Rare: Stomatitis, gastrointestinal candidiasis, dry mouth, microscopic colitis.

Very Rare: Dyspepsia, haemorrhagic necrotic gastritis (*reported in children*).

Hepatobiliary disorders

Uncommon: Increased liver enzymes.

Rare: Encephalopathy in patients with pre-existing severe liver disease, hepatitis with or without jaundice, hepatic failure.

Skin and subcutaneous tissue disorders

Uncommon: Rash, urticaria, pruritus, dermatitis.

Rare: Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia.

Not known: Subacute cutaneous lupus erythematosus (SCLE).

Musculoskeletal connective tissue and bone disorders

Rare: Arthralgia, muscular weakness, myalgia.

Renal and urinary disorders

Rare: Interstitial nephritis.

Very Rare: Impaired renal function, including nephrosis.

Reproductive system and breast disorders

Rare: Gynaecomastia.

Very Rare: Impotence (although causality has not been established).

General disorders and administration site conditions

Uncommon: Malaise.

Rare: Increased sweating, peripheral oedema.

DOSAGE AND ADMINISTRATION

Chemmart Omeprazole enteric coated tablets must be swallowed whole (not broken or chewed) with liquid.

Chemmart Omeprazole is only available as 20 mg enteric coated tablet which must not be broken. For 10 mg dosing, another brand of omeprazole with a 10 mg dose strength should be used.

Symptomatic GORD

Recommended dose for symptom relief: omeprazole 10–20 mg once daily for a maximum of 4 weeks.

In most patients symptom relief is rapid. If symptom control has not been achieved after 4 weeks treatment with omeprazole 20 mg daily, further investigation is recommended.

Erosive Oesophagitis

Recommended healing dosage: omeprazole 20 mg once daily for 4–8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks. For those patients not fully healed on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further 4 weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, omeprazole 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

It is recommended that, after healing, maintenance therapy be commenced, omeprazole 10 mg once daily. If needed, this dose should be increased to omeprazole 20 mg once daily.

Peptic Ulcer Disease Associated with *Helicobacter pylori* Infection

Patients whose gastric or duodenal ulceration is not associated with ingestion of NSAIDs require treatment with antimicrobial agents, in addition to antisecretory drugs, whether on first presentation or on recurrence. Omeprazole administered at a dose of 40 mg once daily or 20 mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- Amoxicillin 500 mg and metronidazole 400 mg both 3 times a day, for 2 weeks; or
- Amoxicillin 1 g and clarithromycin 500mg both twice a day, for 1 week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day, for 1 week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. In this situation, possible resistance of the organism to the antimicrobial agents should be considered when deciding on the combination to be used.

To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for duodenal and gastric ulcer.

Duodenal Ulcer

Recommended Healing Dosage

Omeprazole 20 mg once daily for 4–8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In duodenal ulcer patients refractory to treatment, omeprazole 40 mg once daily usually produces healing within 4–8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with duodenal ulcer who are proven to be *H. pylori* negative and whose ulceration had not been associated with NSAIDs, the recommended dose is omeprazole 10–20 mg daily.

For NSAID-associated duodenal ulcers, see **NSAID-Associated Gastric or Duodenal Ulcers or Erosions**, below.

Gastric Ulcer

Recommended healing dosage: omeprazole 20 mg once daily for 4–8 weeks.

In most patients, symptomatic relief is rapid and healing is usually complete within 4 weeks.

For those patients not fully healed during initial treatment, healing usually occurs during a further 4 weeks treatment period.

In gastric ulcer patients refractory to treatment, omeprazole 40 mg once daily usually produces healing within 8 weeks.

Maintenance Therapy

For the long-term prevention of relapse in patients with gastric ulcer who are proven to be *H. pylori* negative and whose ulceration had not been associated with NSAIDs, the recommended dose is omeprazole 20 mg daily.

For NSAID-associated duodenal ulcers, see **NSAID-Associated Gastric or Duodenal Ulcers or Erosions**, below.

NSAID-Associated Gastric or Duodenal Ulcers or Erosions

In patients with or without continued NSAID treatment, the recommended dose is omeprazole 20–40 mg daily. Symptom resolution is rapid and healing occurs within 4 weeks in most patients.

For those patients not fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

For the prevention of NSAID-associated gastric or duodenal ulcers or erosions and dyspeptic symptoms, the recommended dose is omeprazole 20 mg once daily.

Zollinger-Ellison Syndrome

Recommended initial dose: omeprazole 60 mg once daily.

The dosage should be adjusted individually and treatment continued for as long as is clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20–120 mg daily. When doses exceed 80 mg orally daily, the dose should be divided and given twice daily.

Use in the Elderly

No dosage adjustment of omeprazole is necessary in the elderly.

Hepatic Insufficiency

The rate of plasma elimination of omeprazole and its metabolites is decreased in patients with liver cirrhosis. However, no accumulation has been observed during the use of the recommended dose of omeprazole 20 mg daily and no adjustment to the normal dosage regime is required (see **PRECAUTIONS**).

Renal Insufficiency

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function and no dosage adjustment is required.

OVERDOSAGE

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to omeprazole 2,400 mg (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole.

Also apathy, depression and confusion have been described in single cases. The symptoms described in connection to omeprazole overdosage have been transient, and no serious clinical outcome due to omeprazole has been reported.

The rate of elimination was unchanged (first-order kinetics) with increased doses and no specific treatment has been needed.

In suspected cases of overdosage treatment should be supportive and symptomatic.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Chemmart Omeprazole enteric-coated tablets are intended for oral administration.

Each enteric-coated tablet contains 20 mg omeprazole as the active ingredient.

Red brown, oblong, enteric-coated tablet.

Blister Pack (aluminium/aluminium) of 5, 10 or 30 enteric-coated tablets (AUST R 243814).

Bottle (white, round HDPE) of 30 enteric-coated tablets (AUST R 243815).

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE

ARTG)

1 December 2011

DATE OF MOST RECENT AMENDMENT

30 January 2017