

## NAME OF THE MEDICINE

APO-OMEPRAZOLE is a proton pump inhibitor.

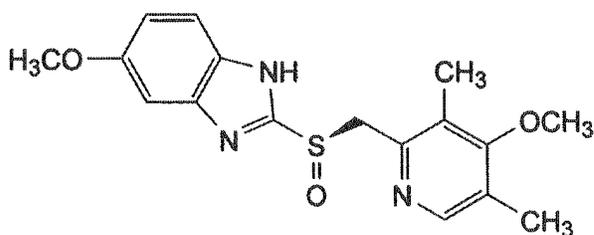
Active Ingredient: Omeprazole.

Chemical name: *(RS)*-5-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole.

Molecular formula: C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S.

MW: 345.5.

CAS: 73590-58-6.



C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S

**Omeprazole**

## DESCRIPTION

Omeprazole is a white to off white powder, very slightly soluble in water, soluble in ethanol, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

### Composition

Active. Omeprazole.

Inactive. Pellets. Sodium lauryl sulfate, sodium phosphate - dibasic anhydrous, hypromellose, mannitol, macrogol, talc - purified, polysorbate 80, titanium dioxide, Eudragit L30-D-55, maize starch and sucrose.

Capsule. Gelatin, titanium dioxide and quinoline yellow CI47005.

## PHARMACOLOGY.

Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H<sup>+</sup>, K<sup>+</sup>-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 one hour and is maximal within two hours. With repeated once daily dosing the maximum effect is usually achieved within four 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 three to five 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 NSAID ingestion. (See **Dosage and Administration**).

*In vitro* testing has shown that omeprazole has an MIC<sub>90</sub> of 25µg/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 two to four-fold during treatment with omeprazole. Up to 3% of patients have values exceeding 400 pg/mL.

## **Pharmacokinetics**

### ***Absorption***

Omeprazole is acid labile and is administered orally as enteric coated granules in capsules. The enteric coating film, protecting the omeprazole, dissolves at a pH above 5.5. Hence omeprazole is not released until the pellets are emptied into the duodenum.

Once omeprazole dissolves in this near neutral environment, the omeprazole ion transforms to its neutral form. The same form of omeprazole is available for absorption regardless of it being administered as the free form, omeprazole, or the salt, omeprazole magnesium.

Absorption is rapid with peak plasma levels of omeprazole occurring within four hours and is usually complete within three to six hours. The systemic bioavailability of omeprazole from a single oral dose of APO-OMEPRAZOLE 20 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 sulphone.

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

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. The 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 (eg. 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 hydroxy-omeprazole and the corresponding carboxylic acid.

**Pharmacokinetics in children**

Available data from children ( $\geq 1$  year) suggest that the pharmacokinetics, within the recommended dosages, is similar to that reported in adults.

**CLINICAL TRIALS**

**Gastro-Oesophageal Reflux Disease (GORD).**

**1. Symptomatic GORD.**

Randomised controlled clinical trials (n=1710) were evaluated to assess the efficacy of omeprazole in the complete relief of heartburn in adult patients with symptomatic GORD after four 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 four weeks is presented in Table 1 below.

Table 1 Percentage patients with complete relief of heartburn after 4 weeks.

Study	Treatment Group (n)	Relief (%) Patients	Group Difference		
				%	95%CI
Lind	Placebo (105)	13	Omeprazole 10 - Placebo	18	9,27
	Omeprazole 10mg (199)	31	Omeprazole 20 - Placebo	33	23,43
	Omeprazole 20mg (205)	46	Omeprazole 20 - Omeprazole 10	15	6,25
Venables	Ranitidine (135)	36	Omeprazole 10 - Ranitidine	0.2	-12,12
	Omeprazole 10mg (126)	36	Omeprazole 20 - Ranitidine	3.7	-8,15
	Omeprazole 20mg (130)	39	Omeprazole 20 - Omeprazole 10	3.5	-8,15
Bate	Placebo (58)	22	Omeprazole 20 - Placebo	36	17,55
	Omeprazole 20mg (48)	58			

CI = confidence interval

## **2. Erosive Oesophagitis**

At the time of registration, seven randomised controlled clinical trials (n=1674) 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 bd or placebo at six 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=1154), 72% and 82% of patients remained in remission at six 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 three 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 two 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 to 12 months, 77 patients completing 18 months, and 208 patients completing two years of continuous omeprazole treatment. Additionally, in open studies at least 109 patients were assessed by annual biopsy during continuous treatment for four years, and in this continuing study, biopsies are available for at least 14 patients treated for up to eight 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.

## **3. Use in children**

In a trial in 65 children aged 0.5 to 17 years with erosive reflux oesophagitis, an oral omeprazole dose of 2.1 mg/kg/day was required to achieve endoscopic healing in 80% of the 57 patients who completed the study. The duration of treatment was 12 to 60 weeks. Reasons for discontinuing treatment were difficulty in administering the drug or inappropriate inclusion in the study.

In 13 children aged 1 to 17 years, oral omeprazole 0.5 to 0.6 mg/kg/day for eight weeks achieved endoscopic healing in two children with giant gastric ulcer, six children with duodenal ulcer and four out of five children with

oesophagitis.

There are no data on the use of omeprazole in children with less severe gastroesophageal reflux disease.

## **INDICATIONS**

APO-OMEPRAZOLE is indicated for:

### **Gastro-Oesophageal Reflux Disease (GORD)**

1. Symptomatic GORD  
The relief of heartburn and other symptoms associated with GORD.
2. Erosive oesophagitis  
The treatment and prevention of relapse.

### **Peptic Ulcers**

1. The treatment of duodenal and gastric ulcer.
2. Combination therapy for the treatment of peptic ulcer disease associated with *Helicobacter pylori* infection.
3. The treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs.
4. 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.
5. 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 of APO-OMEPRAZOLE.

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

## **PRECAUTIONS**

### ***Undiagnosed malignancy***

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

### ***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**).

### ***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.

#### ***Hepatic Insufficiency***

Patients with impaired liver function have shown a markedly increased bioavailability, a reduced total plasma clearance, and up to a four-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 20 mg omeprazole daily may be used in patients with severe liver disease (see **Dosage and Administration**).

#### ***Antimicrobial resistance***

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

***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*.

***Carcinogenicity, mutagenicity, impairment of fertility***

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 were 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:

- a) Exogenous gastrin infusion. Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL cells following treatment for one month.
- b) H<sub>2</sub>-receptor antagonists. In rats administered 2 g/kg/day of ranitidine 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.

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.

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/m<sup>2</sup> basis). Embryofetal 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 (seven 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 nursing mothers.

***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).

***Metabolism***

***Cytochrome P-450 effects***

Omeprazole is mainly metabolised via the hepatic cytochrome P-450 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 of diazepam dosage when APO-OMEPRAZOLE is co-prescribed.

***Phenytoin***

Omeprazole 40 mg daily for seven days reduced plasma clearance of IV phenytoin by 15 to 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 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 CYP 2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decrease 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**

Results from 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 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 esomeprazole and clopidogrel should be avoided.

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 similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) 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 to 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 and oestradiol).

#### ***Effects of other medicines on omeprazole.***

Drugs known to induce CYP2C19 and 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 and 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 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. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurement. Measurements should be repeated if levels have not normalised by this time.

### **ADVERSE EFFECTS**

Omeprazole is 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  $\geq 1.0\%$  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, agranulocytosis, thrombocytopenia and pancytopenia.

#### ***Immune system disorders***

Rare: hypersensitivity reactions (eg. Fever, angioedema and anaphylactic reaction/shock.)

#### ***Metabolism and nutrition disorders***

Rare: hyponatraemia.

Very rare: weight increase, hypomagnesaemia, hypokalaemia (reported in children); severe hypomagnesaemia may result in hypocalcaemia.

Hypomagnesaemia may also result in hypokalaemia.

#### ***Psychiatric disorders***

Uncommon: insomnia.

Rare: reversible mental confusion, agitation, aggression, depression and 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: abdominal pain, nausea/ vomiting, constipation, diarrhoea, 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 liver disease; hepatitis with or without jaundice, hepatic failure.

***Skin and subcutaneous skin disorders***

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

***Musculoskeletal, connective tissue and bone disorders***

Rare: muscular weakness, arthralgia and 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**

APO-OMEPRAZOLE should be swallowed whole (not broken or chewed) with liquid. It should be noted that APO-OMEPRAZOLE is only available in 20 mg.

### **Symptomatic GORD.**

Recommended dose for symptom relief;  
Omeprazole 10 mg to 20 mg once daily for a maximum of four weeks.

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

### **Erosive oesophagitis.**

Recommended healing dosage:  
Omeprazole 20 mg once daily for four to eight weeks.

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

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

### ***Maintenance Therapy.***

After healing, it is recommended that maintenance therapy be commenced with 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 non-steroidal anti-inflammatory drugs 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 three times a day for two weeks; or
- Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week; or
- Clarithromycin 250 mg and metronidazole 400 mg twice a day for one 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;

Oral administration of omeprazole 20 mg once daily for four to eight weeks.

In most patients symptomatic relief is rapid and healing is usually complete within four weeks. For those patients not fully healed during the initial four weeks of treatment, healing usually occurs during a further four week treatment period.

In duodenal ulcer patients refractory to treatment, omeprazole 40mg once daily usually produces healing within four to eight 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 non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is omeprazole 10 to 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 four to eight weeks.

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

For those patients not fully healed during the initial four weeks of treatment, healing usually occurs during a further four week treatment period.

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

Symptom resolution is rapid and healing occurs within four weeks in most patients. For those patients not fully healed after the initial course, healing usually occurs during a further four 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 to 120mg daily. When doses exceed 80mg orally daily, the dose should be divided and given twice daily.

**Use in children**

For use in children one year and older the recommended dose is;

<i>Weight</i>	<i>Dose</i>
10-20kg	Omeprazole 10 mg once daily for 2 to 8 weeks
>20kg	Omeprazole 20 mg once daily for 2 to 8 weeks

If needed the dose may be increased to 20 mg and 40 mg respectively.

**Geriatrics**

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 omeprazole daily and no adjustment to the normal dosage regimen 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**

Contact the Poisons Information Centre on 131 126 for advice on management of an overdose.

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.

**PRESENTATION AND STORAGE CONDITIONS**

Each capsule contains omeprazole 20mg in enteric-coated, off-white to cream-white spherical pellets. The pellets are contained in an opaque yellow cap and body, hard gelatin capsules.

Bottle: 5,7,14,15,28,30,50,56,60,90,100 & 500 capsules

Blister: 7,14,15,28,30,50,56,60,90,98,100,140,280 & 500 capsules

**Storage** Store below 25 deg. C. Protect from moisture.

**NAME AND ADDRESS OF THE SPONSOR**

Pharmacor Pty Ltd  
Suite 401, 7 Oaks Ave  
Dee Why NSW 2099  
Australia

**NAME AND ADDRESS OF THE DISTRIBUTOR**

Apotex Pty Ltd  
3/16 Giffnock Avenue  
Macquarie Park NSW 2113  
Australia

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4 (S4) Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC  
GOODS (THE ARTG):**

149518: 7<sup>th</sup> July 2009 (blister), 167316: 9<sup>th</sup> April 2010 (bottle)

**DATE OF MOST RECENT AMENDMENT**

31 October 2014