

PRODUCT INFORMATION

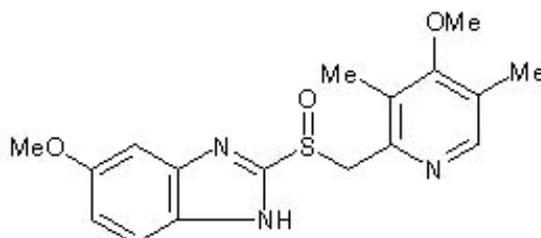
OMEPRAZOLE SANDOZ[®] 20MG ENTERIC CAPSULES

NAME OF THE MEDICINE

Active: Omeprazole

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

Chemical Structure:



Molecular Formula: C₁₇H₁₉N₃O₃S *Molecular Weight:* 345.4

CAS: 73590-58-6

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.

Inactive: Pellets: Sodium lauryl sulfate, dibasic anhydrous sodium phosphate, hypromellose, mannitol, macrogol 6000, purified talc, polysorbate 80, titanium dioxide, Eudragit L30-D-55 (ARTG No. 3700), maize starch and sucrose.

Capsule: gelatin, titanium dioxide and quinoline yellow CI47005.

PHARMACOLOGY

Pharmacological Actions

Omeprazole belongs to the group of drugs known as proton pump inhibitors. It acts to reversibly reduce gastric acid secretion by inhibiting the enzyme H⁺,K⁺-ATPase in the acid environment of the intracellular canaliculi within the parietal cell. Omeprazole has a dose dependent effect on the final step of the gastric acid formation process. Basal acid secretion and stimulated acid secretion are both effectively inhibited by omeprazole.

No clinically significant pharmacodynamic effects have been observed apart from those explained by the effect of omeprazole on acid secretion. Omeprazole has no effect on histamine or acetylcholine receptors.

Oral administration of omeprazole 20mg once a day provides a rapid and effective reduction of gastric acid secretion beginning within one hour and is maximal within two hours of a single dose. Repeated once daily dosing achieves its maximal effect within four days of the start of treatment.

Helicobacter pylori is the major factor in the development of gastritis and ulcer in patients with duodenal and gastric ulcer disease. *Helicobacter pylori* is associated with about 95% of patients suffering from duodenal ulcer disease and 70% of patients with gastric ulcer disease. Recent evidence has also suggested 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). Successful eradication of *H. pylori* is associated with a reduced incidence of peptic ulcer recurrence.

Any attempt to eradicate *H. pylori* requires combined treatment with omeprazole and antimicrobial agents. Omeprazole was shown to have a MIC₉₀ of 25microgram/mL against *H.pylori in vitro*. However, its action *in vivo* results only in the suppression of *H. pylori* not its eradication. Results have shown that the use of antimicrobial agents alone has been ineffective in eradicating the organism. The eradication rates for *H. pylori* are optimal when omeprazole is combined with two antimicrobial agents, although the exact mechanism of the synergy between omeprazole and antimicrobial agents is not understood.

Duodenal ulcer patients treated with an oral dose of omeprazole 20mg maintain an average reduction in 24 hour intragastric acidity of approximately 80%. Omeprazole produces a mean decrease of approximately 70% in peak pentagastrin stimulated acid output 24 hours after dosing. Secretory activity returns to approximately 50% of maximum 24 hours after discontinuation of omeprazole, and then gradually returns to normal over three to five days.

Other effects related to 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.

A two to fourfold increase in fasting serum gastrin levels has been noted during treatment with omeprazole in some patients with up to 3% of patients having values in excess of 400picogram/mL.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Pharmacokinetics

Omeprazole is administered orally as enteric coated granules in capsules since it is acid labile. Omeprazole is rapidly absorbed, with peak plasma levels occurring within four hours, and is usually complete within three to six hours. Following a single oral dose the systemic bioavailability of omeprazole is approximately 35%, with repeated once daily administration increasing bioavailability to about 60%. Food has no effect on the oral bioavailability of omeprazole but the rate of absorption may be reduced. Omeprazole is approximately 95% bound to plasma proteins.

The average half-life of the terminal phase of the plasma concentration time curve is approximately 40 minutes following intravenous administration of omeprazole; total plasma

clearance is 0.3 to 0.6L/minute. During repeated dosing the half-life is not altered. The inhibitory effect of omeprazole on 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.

The liver is the main site of metabolism for omeprazole. The metabolites identified in plasma following the complete metabolism of omeprazole are the sulfone, the sulfide and hydroxyomeprazole. These metabolites do not have a significant effect on acid secretion. About 80% of the metabolites are renally cleared with the two main urinary metabolites being hydroxyomeprazole and the corresponding carboxylic acid. The remaining metabolites are excreted in the faeces.

In a single-dose, four-way crossover study in 48 subjects, Omeprazole Sandoz® (omeprazole) 20mg enteric capsules were found to be bioequivalent to Losec® (omeprazole magnesium - AstraZeneca) 20mg tablets, under fed and fasting conditions.

CLINICAL TRIALS

Gastro-Oesophageal 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 four weeks treatment comparing omeprazole 10mg and 20mg once daily with control groups of ranitidine 150mg twice daily or placebo.

The percentage of patients with complete relief of heartburn after four weeks is presented below:

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

Plac = placebo; Ome = omeprazole; Ranit = ranitidine

Erosive Oesophagitis

The efficacy of omeprazole in the prevention of relapse in patients with healed reflux oesophagitis has been assessed and evaluated in seven randomised controlled clinical trials (n = 1,674). Once daily doses of omeprazole 10mg and omeprazole 20mg maintained endoscopic remission rates which substantially exceeded those of ranitidine 150mg twice a day or placebo at six months. The difference in remission rates favoured omeprazole 20mg over omeprazole 10mg. Remission rates

were recorded over twelve months in three studies and an additional study continued for 18 months.

In a meta-analysis of five of the clinical trials (n = 1,154), 72% of patients on omeprazole 10mg once daily and 82% of patients on omeprazole 20mg once daily, remained in remission at six months. In a separate large study (n = 327), once daily dosing of omeprazole 10mg for 18 months had a remission rate of 60%. In two of the studies, patients on maintenance therapy who relapsed in the first three months of treatment were then healed and treated with a maintenance dose of omeprazole 20mg. The difference in the total remission rate over 6 or 12 months indicates that it may take longer or be more difficult to obtain subsequent healing and control if omeprazole 10mg had been used rather than 20mg for initial maintenance therapy.

Due to histological changes observed in animals a full analysis of gastric safety data from seven controlled clinical trials was undertaken (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 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. There have been no instances of dysplasia or carcinoids of the gastric enterochromaffin-like (ECL) cells 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

- The relief of heartburn and other symptoms associated with GORD.
- Treatment and prevention of relapse in erosive oesophagitis.
- Treatment of duodenal and gastric ulcer.
- Combination therapy for the treatment of peptic ulcer disease associated with *H. pylori* infection.
- Treatment of gastric and duodenal ulcers and erosions associated with non-steroidal anti-inflammatory drugs (NSAIDs).
- Prevention of gastric and duodenal ulcers and erosions associated with NSAIDs 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 *H. pylori* negative or in whom eradication is inappropriate (e.g. the elderly) or ineffective.
- Treatment of Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Hypersensitivity to omeprazole, substituted benzimidazoles or any other ingredient of Omeprazole Sandoz[®].

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 (eg. 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.

Impaired hepatic function

Patients with impaired hepatic function have shown a marked increase in bioavailability, a reduction in total plasma clearance and an up to fourfold increase in the elimination half-life of omeprazole. However, urinary recovery over 96 hours remains unchanged, indicating that there is no accumulation of omeprazole or its metabolites. The normal dose of omeprazole 20mg a day may be used in patients with severe hepatic disease (see DOSAGE AND ADMINISTRATION).

Antimicrobial resistance

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

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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 20mg 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.

Effects related to 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*.

For long-term treatment

Cyanocobalamin (vitamin B-12) deficiency

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy. Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors like omeprazole.

Hypomagnesaemia

Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the proton pump inhibitor.

For patients expected to be on prolonged treatment or who take proton pump inhibitors with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting proton pump inhibitor treatment and periodically during treatment.

Osteoporotic fractures

Proton pump inhibitors, especially if used in high doses and over long durations, may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Patients on long terms treatment should be kept under regular surveillance.

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.

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 320mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40mg/day, based on plasma AUC) and 100mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40mg/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 embryofoetal toxicity.

Use in pregnancy (Category B3)

Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Results from three prospective epidemiological studies indicate that while 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 40mg/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 138mg/kg/day and above (seven-fold anticipated exposure at the clinical dose of 40mg/day, based on plasma AUC) and intravenous doses of 3.2mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in breast-feeding mothers.

Paediatric use

There is no experience with Omeprazole Sandoz[®] in children.

Genotoxicity

A range of genotoxicity tests, *in vitro* and *in vivo*, have been used to examine the mutagenic, clastogenic and DNA-damaging potential of omeprazole. 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 observed in the tests used.

Carcinogenicity

In a two year carcinogenicity study involving male and female rats, omeprazole at doses of 13.8, 44.0 and 140.8mg/kg/day produced gastric enterochromaffin-like (ECL) cell hyperplasia and carcinoid tumours in a dose related manner in both sexes. A markedly higher incidence of these effects occurred in female rats. An additional two year study in female rats at doses of 1.7, 3.4 and 13.8mg/kg/day produced the same effects. In the dose ranges studied a no effect dose was not established in female rats.

In a carcinogenicity study performed in mice over 78 weeks, no gastric ECL cell carcinoids were seen. However, longer term studies have not been performed in this species. ECL cell hyperplasia, hypergastrinaemia and gastric carcinoids have also been produced in the rat by other treatments or procedures not related to omeprazole.

These include the following:

Exogenous gastrin infusion. Treatment with a subcutaneous infusion of gastrin-17 for one month produced a significant hyperplasia of ECL cells.

H2-receptor antagonists. Administration of ranitidine 2g/kg/day to rats in their diet over 106 weeks resulted in argyrophilic cell hyperplasia being observed in 37% of the animals, and gastric carcinoids were found in 19% of the treated group.

Surgical resection of the acid producing oxyntic mucosa. In rats which had 75% of the stomach corpus surgically removed, 26 of 75 animals developed ECL cell carcinoids during the 124 week study.

These findings indicate 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.

Other cells in the gastrointestinal tract (e.g. G cells) may also be affected by omeprazole, either directly or by inducing sustained hypochlorhydria, however this possibility has not been extensively studied. (See PHARMACOLOGY)

Effect on ability to drive or operate machinery

No effects have been observed.

Adverse drug reactions such as somnolence, dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

Effects on laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements (see PHARMACOLOGY).

If CgA and gastrin levels have not returned to reference range after initial measurement, measurements, should be repeated 14 days after cessation of proton pump inhibitor treatment.

INTERACTIONS WITH OTHER MEDICINES

Food. Concomitant administration of omeprazole and food does not affect the extent of bioavailability of omeprazole, however, the rate of absorption may be reduced.

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.

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.

Theoretical interactions.

Ketoconazole, itraconazole. 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, may decrease during treatment with omeprazole.

Metabolism.

Cytochrome P450 effects. Omeprazole is metabolised via the hepatic cytochrome P450 system (CYP2C19) and interactions with the pharmacokinetics of other drugs metabolised by this system may be expected.

Potential interactions.

Clopidogrel. Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by omeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore its clinical efficacy. Concomitant use of omeprazole with clopidogrel should be discouraged.

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 40mg, 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).

Demonstrated interactions.

Diazepam. Following dosing with omeprazole 40mg 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 20mg, 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 Omeprazole Sandoz[®] is co-prescribed.

Phenytoin. Omeprazole 40mg daily for seven days reduced plasma clearance of intravenous 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 20mg to epileptic patients, steady state plasma levels of phenytoin were unchanged during omeprazole treatment.

Warfarin. Concomitant administration of omeprazole 20mg and warfarin to healthy volunteers resulted in 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. This stereoselective interaction resulted in a small but statistically significant increase in warfarin's anticoagulant activity.

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

Cilostazol. Omeprazole given in doses of 40mg daily to healthy subjects in a cross over study 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.

St. John's Wort. Because of potential clinically significant interaction, St. John's Wort should not be used concomitantly with omeprazole.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin) 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.

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

Clarithromycin. Omeprazole and clarithromycin plasma concentrations are increased during concomitant administration.

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.

Atazanavir, nelfinavir. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole.

Saquinavir. 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.

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

Digoxin. 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). Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

ADVERSE EFFECTS

Omeprazole is well tolerated. Most adverse effects have been mild and transient and there has been no consistent relationship with treatment.

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing.

Adverse reaction 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:

Dermatological

Uncommon: rash, pruritus and/or urticaria, dermatitis alopecia, photosensitivity, erythema multiforme, skin eruptions.
Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN).
Not known: Subacute cutaneous lupus erythematosus (see PRECAUTIONS)

Musculoskeletal

Uncommon: Fracture of the hip, wrist or spine
Rare: muscular weakness, arthralgia, and myalgia.

Central and peripheral nervous system

Common: headache, somnolence, insomnia.
Uncommon: dizziness, paraesthesia.
Rare: reversible mental confusion, agitation, aggression, light-headedness, depression and hallucinations, predominantly in severely ill patients or elderly patients.

Gastrointestinal

Common: abdominal pain, nausea/vomiting, constipation, diarrhoea, flatulence.
Uncommon: taste disturbances. These conditions usually resolve on cessation of therapy.
Rare: stomatitis, gastrointestinal candidiasis, microscopic colitis and dry mouth.
Very rare: dyspepsia, haemorrhagic necrotic gastritis (reported in children).

Hepatic

Uncommon: increased liver enzymes.
Rare: encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure.

Endocrine

Rare: gynaecomastia.
Very rare: impotence (although causality has not been established).

Haematological

Rare: hypochrome, microcytic anaemia in children, leucopenia, agranulocytosis, thrombocytopenia and pancytopenia.

Eye disorders

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Other

Uncommon: malaise, peripheral oedema, increased sweating.
Rare: hypersensitivity reactions, e.g. bronchospasm, angioedema, fever, interstitial nephritis, anaphylactic shock, blurred vision, taste disturbance and hyponatraemia.
Very rare: elevated body temperature, allergic vasculitis, impaired renal function, including nephrosis, dyspnoea, weight increase, hypomagnesaemia and hypokalaemia (reported in children).

DOSAGE AND ADMINISTRATION

Omeprazole Sandoz[®] should be swallowed whole with water. It should be noted that Omeprazole Sandoz[®] is only available in 20mg.

- *Symptomatic GORD. Recommended dose for symptom relief.* Omeprazole 10mg to 20mg 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 Omeprazole Sandoz[®] 20mg daily, further investigation is recommended.

- *Erosive oesophagitis. Recommended healing dosage.* Omeprazole 20mg 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, a further four week treatment period usually results in endoscopic healing.

Omeprazole 40mg once daily usually produces healing within eight weeks in patients with ulcerative reflux oesophagitis refractory to treatment.

Maintenance. After healing, it is recommended that maintenance therapy be commenced with omeprazole 10mg once daily. If needed, this dose should be increased to omeprazole 20mg once daily.

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

Amoxicillin 500mg and metronidazole 400mg both three times a day for two weeks; or

Amoxicillin 1g and clarithromycin 500mg both twice a day for one week; or

Clarithromycin 250mg and metronidazole 400mg twice a day for one week.

Patients should be retreated if there is a return of symptoms and *H. pylori* infection. The possibility of resistance of the organism to the antimicrobial agents should be taken into consideration when deciding on the combination to be used in this situation 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. In those patients not fully healed during the initial four weeks of treatment, healing usually occurs during a further four weeks of treatment.

Omeprazole 40mg once daily usually produces healing within four to eight weeks in patients with duodenal ulcer refractory to treatment.

Maintenance. For the long term prevention of relapse in patients with duodenal ulcer who are proven to be *Helicobacter pylori* negative and whose ulceration had not been associated with

non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is omeprazole 10mg to 20mg daily.

For NSAID-associated duodenal ulcers see *NSAID-associated gastric or duodenal ulcers or erosions*.

- *Gastric ulcer. Recommended healing dosage.* Omeprazole 20mg 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 during the initial four weeks of treatment, healing usually occurs during a further four weeks of treatment. Omeprazole 40mg once daily usually produces healing within eight weeks in patients with gastric ulcer refractory to treatment.

Maintenance. The recommended dose 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 is omeprazole 20mg daily.

For NSAID-associated duodenal ulcers see *NSAID-associated gastric or duodenal ulcers or erosions*.

- *NSAID-associated gastric or duodenal ulcers or erosions.* The recommended dose in patients with or without continued NSAID treatment is omeprazole 20 to 40mg daily.

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

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

- *Zollinger-Ellison syndrome. Recommended initial dose:* Omeprazole 60mg once daily. The dosage should be adjusted to the individual patient's response and treatment continued for as long as is clinically indicated. Effective control has been achieved for more than 90% of patients with severe disease and inadequate response to other therapies, using dosages ranging from 20 to 120mg daily. Where the daily oral dose exceeds 80mg, omeprazole should be given in divided doses twice daily.

Use in impaired hepatic function

The rate of plasma elimination of omeprazole and its metabolites is reduced in patients with hepatic cirrhosis. However, no accumulation of omeprazole or its metabolites has been observed during the use of the recommended dose of omeprazole 20mg daily and no adjustment to the normal dosage regimen is necessary (see PRECAUTIONS).

Use in impaired renal function

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

Use in the elderly

It is not necessary to adjust the dosage of omeprazole for the elderly.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of an overdose.

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560mg have been described and occasional reports have been received when single oral doses have reached up to 2400mg omeprazole (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 transit, 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

Bottle: 30 enteric capsules each containing omeprazole 20mg in enteric-coated, off-white to cream-white spherical pellets. The pellets are contained in an opaque yellow cap & body, hard gelatin capsules.

Note: Omeprazole Sandoz[®] is available in 20mg enteric capsules only.

Store below 25°C. Protect from moisture.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park
NSW 2113
Australia
Tel: 1800 634 500

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
27/05/2002

Date of most recent amendment: 04/01/2017