PRODUCT INFORMATION

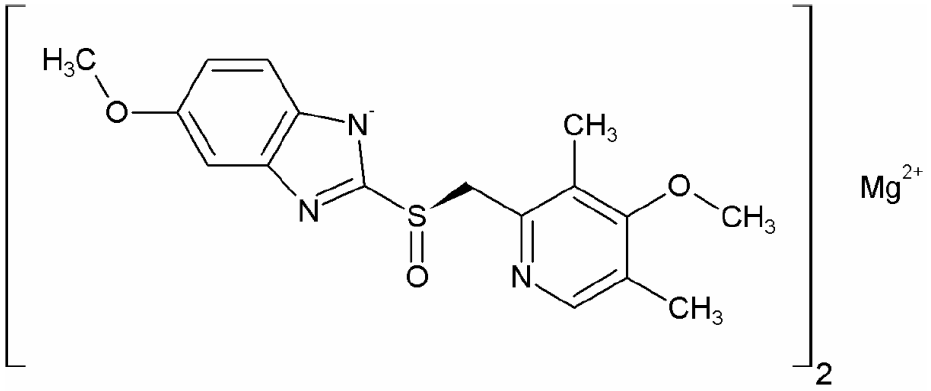
OMEPRAZOLE SANDOZ 10MG AND 20MG ENTERIC-COATED TABLETS

NAME OF THE MEDICINE

Chemical name:
Magnesium bis[5-methoxy-2-[(RS)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-1H-benzimidazol-1-ide]

Generic name: Omeprazole magnesium

Chemical structure:



and enantiomer

CAS [95382-33-5] $C_{34}H_{36}MgN_6O_6S_2$ MW: 713 g/mol

DESCRIPTION

A white or almost white powder, very slightly soluble in water, sparingly soluble in methanol, practically insoluble in heptane. It dissolves in dilute solutions of alkali hydroxides.

In addition to omeprazole magnesium, Omeprazole Sandoz enteric-coated granules in tablets contain sucrose, maize starch, glucose, copovidone, povidone, purified talc, titanium dioxide, methacrylic acid - ethyl acrylate copolymer (1:1), glyceryl monostearate, propylene glycol, stearic acid, polysorbate 80, simethicone, microcrystalline cellulose, macrogol 6000, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, iron oxide red and iron oxide yellow (10mg tablets only).

PHARMACOLOGY

Pharmacodynamics

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 20mg 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 20mg. 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 non-steroidal anti-inflammatory drug (NSAID) ingestion. (See DOSAGE AND ADMINISTRATION.)

In vitro testing has shown that omeprazole has an MIC_{90} (minimum inhibitory concentration) of 25microgram/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.

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.

In some patients, fasting serum gastrin levels have been noted to rise two to fourfold during treatment with omeprazole. Up to 3% of patients have values exceeding 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

Pharmacokinetics in children.
Available data from children (greater than or equal to 1 year) suggests that the pharmacokinetics, within the recommended dosages, are similar to those reported in adults.

Absorption.
Omeprazole is acid labile and is administered orally as enteric-coated granules in tablets. The enteric-coating film, protecting the omeprazole, dissolves at a pH above 5.5. Hence omeprazole is not released until the tablet is dissolved in the duodenum.

Once omeprazole magnesium 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 omeprazole 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. Identified metabolites in plasma are the sulfone, the sulfide and hydroxy-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 intravenous administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6L/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. 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 (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.

CLINICAL TRIALS

- 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 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 in the table below:

Patients (%) with complete relief of heartburn at four weeks

Study	**Group [n]**	**Relief [% patients]**	**Group difference**	**[%]**	**95% CI**
Lind	Plac (105)	13	Ome 10 – Plac	18	9.27
	Ome 10 (199)	31	Ome 20 – Plac	33	23.43
	Ome 20 (205)	46	Ome 20 – Ome 10	15	6.25
Venables	Ranit (135)	36	Ome 10 – Ranit	0.2	- 12.12
	Ome 10 (126)	36	Ome 20 – Ranit	3.7	- 8.15
	Ome 20 (130)	39	Ome 20 – Ome 10	3.5	- 8.15
Bate	Plac (58)	22	Ome 20 – Plac	36	17.55
	Ome 20 (48)	58			

Plac = placebo; Ome = omeprazole; Ranit = ranitidine

- 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 10mg and 20mg once daily maintained endoscopic remission rates which substantially exceeded ranitidine 150mg twice daily or placebo at six months. The difference in remission rates between omeprazole 10mg and 20mg favoured 20mg. 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 six months on omeprazole 10mg and 20mg once daily, respectively. In a separate large study (n = 327), the remission rate following omeprazole 10mg 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 20mg. The difference in the total remission rate over six or twelve months, while small, suggests that it may be more difficult or take longer to obtain subsequent healing and control if 10mg rather than 20mg 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 six to twelve 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.

- 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 0.6mg/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 gastro-oesophageal reflux disease.

INDICATIONS

Gastro-oesophageal 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 of Omeprazole Sandoz.

Omeprazole like other PPIs should not be administered with atazanavir (see INTERACTIONS WITH OTHER MEDICINES).

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

PRECAUTIONS

Check the following before use:

Undiagnosed malignancy
As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurring vomiting, dysphagia, haematemesis, or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded before therapy

with Omeprazole Sandoz tablets, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Concomitant therapy with clopidogrel
Concomitant use of omeprazole and clopidogrel should be avoided (see INTERACTIONS WITH OTHER MEDICINES).

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 affect on eradication regimens. The clinical impact of this resistance on *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.

Special Patient Population

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.

Impaired hepatic function
Patients with impaired liver function show a markedly increased bioavailability, a reduced total plasma clearance, and up to a fourfold 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 20mg daily may be used in patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

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 possibly also *Clostridium difficile* in hospitalised patients.

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.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors like omeprazole. 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 use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated and also should have an adequate intake of vitamin D and calcium.

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

Carcinogenicity/mutagenicity/impairment of fertility
In a two year carcinogenicity study in rats, omeprazole at daily doses of 13.8, 44.0 and 140.8mg/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 13.8mg/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:

Exogenous gastrin infusion.
Subcutaneous infusion of gastrin-17 has resulted in a significant hyperplasia of ECL cells following treatment for one month.

H2-receptor antagonists.
In rats administered 2g/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.

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 (for example, 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 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 sevenfold clinical exposure was associated with embryofetal 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-fold 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 40mg/day clinical dose (on a mg/m^2 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 138mg/kg/day and above (sevenfold 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.

Effect on ability to drive or operate machinery
No effects have been observed.

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 to fourteen days before CgA measurements. Measurements should be repeated if levels have not normalised by this time.

INTERACTIONS WITH OTHER MEDICINES

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

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 and erlotinib 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). 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.

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.
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 in diazepam dosage when Omeprazole Sandoz tablets are 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 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 International Normalised Ratio (INR) is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

Cilostazol.
Omeprazole 40mg 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 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.

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

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

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 vitro* 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, and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lignocaine, quinidine and oestradiol).

Effects of other drugs on omeprazole.
Demonstrated interactions.
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.
Plasma concentrations of omeprazole are increased during concomitant administration.

ADVERSE EFFECTS

Omeprazole 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: greater than or equal to 10%;
common: greater than or equal to 1% and < 10%;
uncommon: greater than or equal to 0.1% and < 1%;
rare: greater than or equal to 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: Hypersenstivity reactions eg. 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: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
Very rare: Dyspepsia, haemorrhagic necrotic gastritis (reported in children)

Hepatobiliary disorders
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, pruritis, rash, urticaria
Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known: Subacute cutaneous lupus erythematosus (see PRECAUTIONS)

Musculoskeletal, connective tissue and bone disorders
Uncommon: Fracture of the hip, wrist or spine
Rare: Arthralgia, myalgia, muscular weakness

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

Adults
Symptomatic gastroesophageal reflux disease (GORD).
Recommended dose for symptom relief is omeprazole 10 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 20mg daily, further investigation is recommended.

Erosive oesophagitis.
Recommended healing dosage is omeprazole 20mg 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 on endoscopic examination during initial treatment, endoscopic healing usually occurs during a further four weeks treatment period.

In patients with ulcerative reflux oesophagitis refractory to treatment, omeprazole 40mg once daily usually produces healing within eight weeks.
Maintenance therapy. It is recommended that, after healing, maintenance therapy be commenced, omeprazole 10mg once daily. If needed, this dose should be increased to omeprazole 20mg 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 40mg once daily or 20mg twice daily in association with the following combinations has been found to achieve eradication rates of approximately 90%:

- amoxycillin 500mg and metronidazole 400mg both three times a day, for two weeks; or
- amoxycillin 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. 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 is omeprazole 20mg orally 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 initial 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 20mg daily.

For NSAID associated duodenal ulcers see NSAID associated gastroduodenal lesions.

Gastric ulcer.
Recommended healing dosage is omeprazole 20mg 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 initial treatment, healing usually occurs during a further four weeks 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 non-steroidal anti-inflammatory drugs (NSAIDs), the recommended dose is omeprazole 20mg daily.

For non-steroidal anti-inflammatory drug (NSAID) associated duodenal ulcers see NSAID associated gastroduodenal lesions.

NSAID associated gastric or duodenal ulcers or erosions.
In patients with or without continued NSAID treatment, the recommended dose is omeprazole 20 to 40mg 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 20mg once daily.

Zollinger-Ellison syndrome.
Recommended initial dose is omeprazole 60mg 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.

<u>Use in children 1 year and older</u>
For children weighing > 20kg the recommended dose is omeprazole 20mg once daily for 2 to 8 weeks. If needed the dose may be increased to 40mg respectively.

For children weighing 10 to 20kg the recommended dose is omeprazole 10mg once daily for 2 to 8 weeks. If needed the dose may be increased to 20mg.

<u>Use in the elderly</u>
No dosage adjustment of omeprazole is necessary in the elderly.

<u>Use in patients with hepatic impairment</u>
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 20mg omeprazole daily and no adjustment to the normal dosage regime is required (see PRECAUTIONS).

Use in patients with renal impairment
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 13 11 26 for advice on management of overdose.

Symptoms
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 omeprazole 2,400mg (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.

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

PRESENTATION AND STORAGE CONDITIONS

Omeprazole Sandoz 10mg enteric-coated tablets - light pink, oval, biconvex film-coated tablets.
Available in Al/Al blisters packs of 30 enteric-coated tablets.

Omeprazole Sandoz 20mg enteric-coated tablets - pink, oval, biconvex film-coated tablets with a breaking notch on both sides.
Available in Al/Al blisters packs and HDPE bottles with white PP caps of 30 enteric-coated tablets.

Each enteric-coated tablet contains either 10 or 20 mg of omeprazole (as magnesium).

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park
NSW, Australia 2113

Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 08/03/2012

Date of most recent amendment: 04/01/2017