APO-OMEPRAZOLE CAPSULES

NAME OF MEDICINE

Active Ingredient: Omeprazole

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

Omeprazole

Molecular Formula: C₁₇H₁₉N₃O₃S

Molecular Weight: 345.5

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.

PHARMACOLOGY

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

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

Effect on Gastric Acid Secretion

Oral dosing with omeprazole 20 mg once daily provides rapid and effective reduction of gastric acid secretion. After a single dose the onset of antisecretory effect occurs within 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 *Heliocobacter pylori*

*Heliocobacter 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 nonsteroidal anti-inflammatory drug (NSAID) ingestion (see **DOSAGE AND ADMINISTRATION**).

*In vitro* testing has shown that omeprazole has an MIC<sub>90</sub> (minimum inhibitory concentration) of 25 microgram/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* Associated with Reduced Peptic Ulcer Recurrence**

**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.

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 400 picogram/mL.

**Pharmacokinetics**

**Pharmacokinetics in Children**

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

**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.

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 mg 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 hydroxyomeprazole. These metabolites have no significant effect on acid secretion. The average half-life of the terminal phase of the plasma concentration time curve following intravenous administration of omeprazole is approximately 40 minutes; the total plasma clearance is 0.3 to 0.6 L/minute. There is no change in half-life during repeated dosing.
**Excretion**
About 80% of the metabolites are excreted in urine and the remainder in faeces. The two main urinary metabolites are hydroxyomeprazole and the corresponding carboxylic acid.

**CLINICAL TRIALS**
**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 10 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.

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

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

CI = Confidence Interval

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

In a meta-analysis of five of the clinical trials (n = 1,154), 72 and 82% of patients remained in remission at six months on omeprazole 10 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.

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
- The relief of heartburn and other symptoms associated with GORD.
- The treatment and prevention of relapse in erosive oesophagitis.
- The treatment of duodenal and gastric ulcer.
- Combination therapy for the treatment of peptic ulcer disease associated with H. 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 H.
  pylori negative, or in whom eradication is inappropriate, e.g. the elderly or ineffective.
- The treatment of Zollinger-Ellison syndrome.

CONTRAINDICATIONS
Hypersensitivity to omeprazole or any other ingredient of APO-Omeprazole Capsules (see
PRESENTATION AND STORAGE CONDITIONS).

Omeprazole like other proton pump inhibitors (PPIs) should not be administered with atazanavir (see
PRECAUTIONS, Interactions).
PRECAUTIONS

Undiagnosed Malignancy
As with all anti-secretory 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.

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.

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 20 mg a day may be used in patients with severe hepatic disease (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a two year carcinogenicity study involving male and female rats, omeprazole at 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 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 13.8 mg/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 2 g/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).

Mutagenicity
A range of genotoxicity tests, in vitro and in vivo, have been used to examine the mutagenic, clastogenic and DNA damaging potential of omeprazole. No evidence of significant genotoxicity was observed in the tests used.
Impairment of Fertility
There was no evidence of an adverse effect on fertility following administration of omeprazole to male and female rats at doses up to 320 mg/kg/day orally (16-fold anticipated exposure at the clinical oral dose of 40 mg/day, based on plasma AUC) and 100 mg/kg/day intravenously (14-fold anticipated exposure at the clinical intravenous dose of 40 mg/day, based on plasma AUC). Oral administration to male rats prior to mating and to female rats prior to and throughout gestation at sevenfold clinical exposure was associated with embryofetal toxicity.

Use in Pregnancy
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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal 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 40 mg/day (based on plasma AUC). Studies in rats did not demonstrate embryotoxicty 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). 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 (sevenfold anticipated exposure at the clinical dose of 40 mg/day, based on plasma AUC) and intravenous doses of 3.2 mg/kg/day and above (less than clinical exposure). It is recommended that omeprazole not be used in breastfeeding mothers.

Use in Children
There is no experience with APO-Omeprazole in children.

Effect on Ability to Drive or Operate Machinery
No effects have been observed.

Interactions
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 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, may decrease during treatment with omeprazole.
**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 that have been Excluded**

*In vitro* interaction studies with omeprazole versus other drugs indicate that omeprazole 20 to 40 mg, given repeatedly, does not influence any other relevant isozymes 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). *In vivo* interaction studies have been performed with omeprazole and the drugs noted above, except phenacetin and oestradiol.

**Effect of Omeprazole on Other Medicines**

**Demonstrated Interactions**

**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 intravenous phenytoin by 15 to 20% and increased the elimination half-life by 27%. It is recommended that plasma concentration of phenytoin be monitored in patients co-prescribed with APO-Omeprazole and phenytoin. 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 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.

**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.

**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.
**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.

**Effect of Other Medicines on Omeprazole**

**Demonstrated Interactions**

**Voriconazole**

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

**Clarithromycin**

Omeprazole plasma concentrations are increased during concomitant administration.

**ADVERSE EFFECTS**

Omeprazole is well tolerated. Most adverse effects 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 1.0% 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:

**Dermatologica**

Uncommon: Rash, pruritus and/or urticaria, dermatitis, alopecia, photosensitivity, erythema multiforme, skin eruptions.

Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN).

**Musculoskeletal**

Rare: Muscular weakness, arthralgia and myalgia.

**Central and Peripheral Nervous System**

Common: Headache, somnolence, insomnia, vertigo.

Uncommon: Dizziness, paraesthesia.

Rare: Reversible mental confusion, agitation, aggression, lightheadedness, 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 and dry mouth. Brownish/ black discoloration of the tongue during concomitant administration of clarithromycin and benign glandular cysts; both were reversible after cessation of treatment.

Very Rare: Pancreatitis, 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:  Hypochromic, microcytic anaemia in children, leucopenia, agranulocytosis, thrombocytopenia and pancytopenia.

Eye Disorders
Uncommon:  Visual disturbances (blurred vision, loss of visual acuity or reduced field of vision). These conditions usually resolve on cessation of therapy.

Ear and Labyrinth Disorders
Uncommon:  Auditory dysfunction (e.g. tinnitus). These conditions usually resolve on cessation of therapy.

Other
Uncommon:  Malaise, peripheral oedema, increased sweating.
Rare:  Hypersensitivity reactions, e.g. bronchospasm, angioedema, fever, interstitial nephritis, anaphylactic shock and hyponatraemia.
Very Rare:  Elevated body temperature, allergic vasculitis, impaired renal function, including nephrosis, dyspnoea, weight increase and hypokalaemia (reported in children).

DOSAGE AND ADMINISTRATION
APO-Omeprazole should be swallowed whole with water. It should be noted that APO-Omeprazole is only available in 20 mg.

Symptomatic GORD
Recommended Dose for Symptom Relief
Omeprazole 10 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 20 mg 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, a further four week treatment period usually results in endoscopic healing.

Omeprazole 40 mg 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 10 mg once daily. If needed, this dose should be increased to omeprazole 20 mg 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 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%.

Amoxycillin 500 mg and metronidazole 400 mg both three times a day for two weeks; or amoxycillin 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. 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.

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

**Maintenance**

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

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

**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 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**

The recommended dose in patients with or without continued NSAID treatment is omeprazole 20 to 40 mg 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 20 mg once daily.
Zollinger-Ellison Syndrome

Recommended Initial Dose

APO-Omeprazole 20 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 120 mg daily. When doses exceed 80mg orally daily, the dose should be divided and given 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 20 mg daily and no adjustment to the normal dosage regimen is necessary (see PRECAUTIONS, Impaired Hepatic Function).

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 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

APO-Omeprazole 20 mg Capsules

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

Blister packs of 7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100, 140, 280 & 500 capsules: AUST R 149518.

Bottles of 5, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100 & 500 capsules: AUST R 167316.

APO-Omeprazole capsules are intended for oral administration. Each capsule contains 20 mg omeprazole, as the active ingredient. In addition, each capsule contains the following inactive ingredients:

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.

Store below 25°C. Protect from moisture.
NAME AND ADDRESS OF THE SPONSOR
Pharmacor Pty Ltd
5/36 Campbell Avenue
Cromer NSW 2099
Australia

NAME AND ADDRESS OF THE DISTRIBUTOR
Apotex Pty Ltd
66 Waterloo Road
North Ryde NSW 2113
Australia

POISONS SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine.

Date of TGA approval: 16 February 2010