

NEW ZEALAND DATASHEET

Probitor

Omeprazole Ph Eur, modified release capsule, 20 mg

Presentation

Capsule, modified release, Size 2, opaque yellow cap and body. Each capsule contains omeprazole 20 mg. This product is not able to deliver all approved dose regimes.

Uses

Actions

Omeprazole, a racemic mixture of two active enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is fast acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Pharmacotherapeutic group

A02BC01 - Selective proton pump inhibitor, substituted benzimidazole, omeprazole.

Mechanism of action

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H⁺,K⁺-ATPase, the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of the stimulus.

Pharmacodynamic effects

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Onset and duration of action

Effect on gastric acid secretion

Oral dosing with omeprazole once daily provides for rapid and effective inhibition of day time and night time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24 hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% twenty four hours after dosing. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

Effect on intragastric pH

Oral dosing with omeprazole 20 mg maintains the intragastric pH at 3 or above for a mean time of 17 hours of the 24 hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces or normalises acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease.

No tachyphylaxis has been observed during treatment with omeprazole.

Effect on Helicobacter pylori

Helicobacter pylori is associated with acid peptic disease, including duodenal and gastric ulcer disease, in which about 95% and 70% of patients respectively are infected with this bacterium. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* has been found to play a causal role in the development of gastric carcinoma.

Omeprazole has a bactericidal effect on *H. pylori in vitro*. Clinical evidence indicates a dose-related synergistic effect between omeprazole and appropriate antibiotics, especially amoxicillin and clarithromycin, in achieving eradication of *H. pylori*. Eradication of *H. pylori* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease. This outcome reduces complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

Other effects related to acid inhibition

During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, 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 a slightly increased risk of gastrointestinal infections from pathogens such as *Salmonella*, *Campylobacter* and possibly also *Clostridium difficile* in hospitalised patients.

Pharmacokinetics

Absorption

Omeprazole is acid labile and is therefore administered orally as enteric-coated pellets in capsules. Absorption takes place in the small intestine and is usually completed within 3 to 6 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 40%. After repeated once daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on the bioavailability.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 litres/kg and a similar value is also seen in patients with renal insufficiency. In elderly patients, and in patients with hepatic insufficiency, the volume of distribution is slightly decreased. The plasma protein binding of omeprazole is about 95%.

Biotransformation

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase), responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates.

No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an orally given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from bile secretion.

The following parameters reflect mainly the pharmacokinetics in individuals considered extensive metabolisers with functional CYP2C19 enzymes.

Elimination

Total plasma clearance is about 30 to 40 litres/hour after a single dose. After both single and repeated

oral once daily dosing, the plasma elimination half-life of omeprazole is usually shorter than one hour and there is no change in half life during long-term treatment. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g., the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration.

Special patient considerations

Impaired renal function

The systemic bioavailability and elimination of omeprazole is unchanged in patients with reduced renal function.

Impaired hepatic function

Reduced liver function with deficient hepatic metabolism leads to increases in the area under the plasma concentration-time curve, and the elimination half-life. Omeprazole has not shown any tendency to accumulate with once daily dosing.

Children

Available data from children (one year and older) suggest that the pharmacokinetics, within the recommended dosages (refer to [Dosage and administration](#)), are similar to those reported in adults.

Elderly

The metabolism rate of omeprazole is somewhat reduced in elderly subjects aged from 75 to 79 years.

Poor metabolisers

Approximately 3% of the Caucasian population and 15 to 20% of Asian populations lack a functional CYP2C19 enzyme and are termed poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Indications

Treatment of: reflux oesophagitis; duodenal ulcer; gastric ulcer; NSAID-associated gastric and duodenal ulcers or erosions; symptoms of acid related dyspepsia; Zollinger-Ellison syndrome.

Eradication of *Helicobacter pylori*

H. Pylori infection is a recognised factor in the pathophysiology of peptic ulcer disease. For patients showing a positive diagnosis for *H. Pylori*, eradication of the infection is the single most important therapeutic intervention. Accordingly, Probitor should be used as part of combination therapy for the eradication of *H. pylori*.

Maintenance

Maintenance treatment of: reflux oesophagitis; duodenal ulcer; gastric ulcer; Zollinger-Ellison syndrome.

Dosage and administration

Dosage

This product is not able to deliver all approved dose regimes.

Reflux oesophagitis

The recommended dosage is omeprazole 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks' treatment period.

In patients with severe reflux oesophagitis a dose of omeprazole 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the long-term management of patients with healed reflux oesophagitis the recommended dose is omeprazole 10 mg once daily. If needed the dose can be increased to omeprazole 20 to 40 mg once daily.

Severe reflux oesophagitis in children from one year and older

The management of severe reflux oesophagitis should be diagnosed or recommended by a specialist paediatrician or gastroenterologist. The following dosage regime for healing (equivalent to about 1 mg/kg/day) is recommended

<u>Weight:</u>	<u>Omeprazole dosage:</u>
10 to 20 kg	10 mg daily
over 20 kg	20 mg daily

If required, the dosage may be increased to 20 mg and 40 mg respectively.

Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease

Triple therapy regimens

Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg, all twice a day for one week;

or

Omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg), all twice a day for one week;

or

Omeprazole 40 mg once daily with amoxicillin 500 mg three times daily and metronidazole 400 mg three times daily for one week.

Dual therapy regimens

Omeprazole 40 to 80 mg daily with amoxicillin 1.5 g daily in divided doses for two weeks. In clinical studies daily doses of 1.5 to 3 g of amoxicillin have been used. Alternatively, omeprazole 40 mg once daily and clarithromycin 500 mg three times daily for two weeks.

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

In each regimen, if the patient is still *Hp* positive, therapy may be repeated.

Duodenal ulcer

The recommended dosage in patients with an active duodenal ulcer is omeprazole 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 2 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 2 week treatment period.

In patients with poorly responsive duodenal ulcer, omeprazole 40 mg once daily is recommended and healing is usually achieved within 4 weeks.

For the prevention of relapse in patients with duodenal ulcer disease the recommended dose is omeprazole 10 mg once daily. If needed, the dose can be increased to omeprazole 20 to 40 mg once daily.

For NSAID-associated duodenal ulcers refer to NSAID-associated gastroduodenal lesions.

Gastric ulcer

The recommended dosage is omeprazole 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks' treatment period.

In patients with poorly responsive gastric ulcer, omeprazole 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the prevention of relapse in patients with poorly responsive gastric ulcer, the recommended dose is omeprazole 20 mg once daily. If needed, the dose can be increased to omeprazole 40 mg once daily.

For NSAID-associated gastric ulcers refer to NSAID-associated gastroduodenal lesions.

NSAID-associated gastroduodenal lesions

For NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients with or without continued NSAID treatment, the recommended dosage of omeprazole is 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period.

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

Symptoms of acid related dyspepsia

For the 24 hour relief, and prevention of symptoms in patients with epigastric pain or discomfort with or without heartburn and indigestion, the recommended dosage is omeprazole 20 mg once daily in the morning for 14 to 28 days. Patients may respond adequately to 10 mg daily and this dose could be considered as a starting dose. If symptom control has not been achieved after 4 weeks treatment with omeprazole 20 mg daily, further investigation is recommended.

Zollinger-Ellison syndrome

In patients with Zollinger-Ellison syndrome the dosage should be individually adjusted and treatment continued as long as is clinically indicated. The recommended initial dosage is omeprazole 60 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of omeprazole 20 to 120 mg daily. When daily doses exceed 80 mg, the dose should be divided and given twice daily.

Impaired renal function

Dose adjustment is not required in patients with impaired renal function.

Impaired hepatic function

As bioavailability and plasma half-life of omeprazole are increased in patients with impaired hepatic function a daily dose of 10 to 20 mg may be sufficient.

Elderly

Dose adjustment is not required in the elderly.

Administration

Protonix capsules are recommended to be given in the morning and swallowed whole with sufficient liquid. The contents of the capsule should not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food, the capsule can be opened and the contents swallowed directly with half a glass of liquid or after mixing the contents in a slightly acidic fluid e.g. fruit juice, yoghurt or in non-carbonated water. The dispersion should be taken immediately or within 30 minutes. Alternatively patients can suck the capsule and swallow the pellets with liquid. The pellets must not be chewed or crushed.

Contraindications

Known hypersensitivity to omeprazole, substituted benzimidazoles or to any of the inactive ingredients listed in [Further information](#).

Warnings and precautions

Warnings

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

Pregnancy and lactation

Use in pregnancy

Assigned Category B3 by the Australian Drug Evaluation Committee. This category includes medicines 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 no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Use in lactation

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

Effects on ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect.

Other

Preclinical safety data

Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies on rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar pathology has been observed after treatment with H₂-receptor antagonists, proton pump inhibitors and after partial fundectomy suggesting that these changes cannot be a direct effect of any individual medicine.

Adverse effects

Omeprazole is well tolerated and adverse reactions have generally been mild and reversible.

The following adverse events have been reported in the clinical trials programme and post-marketing of omeprazole. None was found to be dose-related and in many cases a causal relationship to treatment with omeprazole has not been established. The reactions are classified according to their reporting frequency.

Common (from 1 in 100 to 1 in 10)

Central and peripheral nervous system: headache.

Gastrointestinal: diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence.

Uncommon (from 1 in 1,000 to 1 in 100)

Central and peripheral nervous system: dizziness, paraesthesia, somnolence, insomnia and vertigo.

Hepatobiliary: increased liver enzymes.

Skin: dermatitis, rash, pruritus, urticaria.

Other: malaise.

Rare (from 1 in 10,000 to 1 in 1,000)

Central and peripheral nervous system: reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.

Endocrine: gynaecomastia.

Gastrointestinal: dry mouth, stomatitis and gastrointestinal candidiasis.

Haematological: leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.

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

Musculoskeletal: arthralgia, muscular weakness and myalgia.

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

Other: hypersensitivity reactions, e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock; increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

Interactions

Medicines and other pharmacologically active substances

The absorption of some medicines might be altered due to the decreased intragastric acidity. The gastric pH-dependent absorption of ketoconazole and itraconazole can decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

As omeprazole is metabolised in the liver predominantly by cytochrome P450 2C19 (CYP2C19), it can prolong the elimination of other substrates for this enzyme such as diazepam, phenytoin, warfarin (R-warfarin) or other Vitamin K antagonists and cilostazol. Concomitant treatment with omeprazole 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with this medicine. Similarly concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin. Nevertheless, monitoring of INR and/or blood levels, as appropriate, is recommended for patients receiving warfarin, other Vitamin K antagonists or phenytoin and a reduction of the phenytoin or anticoagulant dose may be necessary. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Omeprazole is partly metabolised also by CYP3A4, but omeprazole does not inhibit this enzyme. Consequently, omeprazole does not affect the metabolism of drugs metabolised by CYP3A4, such as cyclosporin, lidocaine or lignocaine, quinidine, estradiol, erythromycin, and budesonide.

Results from a range of interaction studies with omeprazole versus other medicines indicate that omeprazole, 20 to 40 mg given repeatedly, has no significant 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).

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus.

Omeprazole has been reported to interact with some antiretroviral medicines. 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 medicine. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral medicines, such as atazanavir and

nelfinavir, decreased serum levels have been reported when given together with omeprazole. Concomitant administration with omeprazole and medicines such as atazanavir and nelfinavir is therefore not recommended. For other antiretroviral medicines, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral medicines of which unchanged serum levels have been reported when given with omeprazole.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration but there is no interaction with metronidazole or amoxicillin. These antimicrobials are used with omeprazole for the eradication of *Helicobacter pylori*.

Since omeprazole is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP 2C19 or CYP 3A4 or both (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of omeprazole's metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. Since high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not required during temporary concomitant use. Medicines known to induce CYP 2C19 or CYP 3A4 or both (such as rifampicin) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

Food and alcohol

No interaction with food or concomitantly administered antacids has been found.

Overdosage

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560 mg have been described and there have been occasional reports of single oral doses up to 2,400 mg omeprazole (120 times the usual recommended clinical dose).

Signs and symptoms

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.

Management

The symptoms described in connection to omeprazole overdosage have been transient, and no serious 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.

Pharmaceutical precautions

Instructions for use/handling

Nil.

Incompatibilities

None known.

Special precautions for storage

Store at or below 25°C. Protect from moisture.

Medicine classification

Prescription Medicine.

Package quantities

Bottles of 30 capsules.

Further information

List of excipients

Sucrose, corn starch, gelatin, polyacrylate dispersion, hydroxypropylmethylcellulose, talc, mannitol, polyethylene glycol, titanium dioxide, polysorbate 80, quinoline yellow, dibasic sodium phosphate, sodium lauryl sulphate.

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