OMARENS

INSTRUCTIONS FOR THE MEDICINAL PRODUCT

Trade name: Omarens.
International Nonproprietary Name: Omeprazole.
Dosage form: Gastro-resistant capsule.
Composition: Each gastro-resistant capsule contains:
Active substance:
Omeprazole 20 mg.
Excipients: Mannitol, Sucrose, Sodium laurilsulfate, Disodium phosphate anhydrous, Sodium methyl parahydroxibenzoate, Sodium propyl parahydroxibenzoate, Hypromellose,
Hypromellose phatalate, Cetyl alcohol, Titanium dioxide, Sugar spheres.
Pharmacotherapeutic group: Proton pump inhibitors.
ATCClassification: A02BC01.
Pharmacologic property:
Pharmacodynamics:
Omeprazole, a racemic mixture of two 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 rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.
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 stimulus.
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.
Pharmacokinetics:
Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.
The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, 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. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.
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).
No metabolite has been found to have any effect on gastric acid secretion.
Special populations:
Impaired hepatic function:
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.
Impaired renal function:
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.
Elderly:
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).
Paediatric patients:
During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.
Indications:
Omarens capsules are indicated for:
Adults:
- Treatment of duodenal ulcers;
- Prevention of relapse of duodenal ulcers;
- Treatment of gastric ulcers;
- Prevention of relapse of gastric ulcers;
- In combination with appropriate antibiotics, Helicobacter pylori (H. pylori) eradication in peptic ulcer disease;
- Treatment of NSAID-associated gastric and duodenal ulcers;
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk;
- Treatment of reflux oesophagitis;
- Long-term management of patients with healed reflux oesophagitis;
- Treatment of symptomatic gastro-oesophageal reflux disease;
- Treatment of Zollinger-Ellison syndrome.

Paediatric use:
Children over 1 year of age and ≥ 10 kg:
- Treatment of reflux oesophagitis;
- Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease.

Children and adolescents over 4 years of age:
- In combination with antibiotics in treatment of duodenal ulcer caused by H. pylori.

Contraindications:
- Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients.
- Omarens like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

Pregnancy and Nursing Mother:
Omarens can be used during pregnancy.
Omarens is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

Dosage and directions for use:
Posology in adults:
Treatment of duodenal ulcers: The recommended dose in patients with an active duodenal ulcer is Omarens 20 mg once daily. In most patients healing occurs within two weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further two weeks treatment period. In patients with poorly responsive duodenal ulcer Omarens 40 mg once daily is recommended and healing is usually achieved within four weeks.
Prevention of relapse of duodenal ulcers: For the prevention of relapse of duodenal ulcer in *H. pylori* negative patients or when *H. pylori* eradication is not possible the recommended dose is Omarens 20 mg once daily. In some patients a daily dose of 10 mg may be sufficient. In case of therapy failure, the dose can be increased to 40 mg.
Treatment of gastric ulcers: The recommended dose is Omarens 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with poorly responsive gastric ulcer Omarens 40 mg once daily is recommended and healing is usually achieved within eight weeks.
Prevention of relapse of gastric ulcers:
For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is Omarens 20 mg once daily. If needed the dose can be increased to Omarens 40 mg once daily.
Treatment of reflux oesophagitis:
The recommended dose is Omarens 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.
In patients with severe oesophagitis Omarens 40 mg once daily is recommended and healing is usually achieved within eight weeks.
Long-term management of patients with healed reflux oesophagitis:
For the long-term management of patients with healed reflux oesophagitis the recommended dose is Omarens 10 mg once daily. If needed, the dose can be increased to Omarens 20-40 mg once daily.
Treatment of symptomatic gastro-oesophageal reflux disease:
The recommended dose is Omarens 20 mg daily. Patients may respond adequately to 10 mg daily, and therefore individual dose adjustment should be considered.
If symptom control has not been achieved after four weeks treatment with Omarens 20 mg daily, further investigation is recommended.
Treatment of Zollinger-Ellison syndrome:
In patients with Zollinger-Ellison syndrome the dose should be individually adjusted and treatment continued as long as clinically indicated. The recommended initial dose is Omarens 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 Omarens 20-120 mg daily. When dose exceed Omarens 80 mg daily, the dose should be divided and given twice daily.
Posology in children:
Children over 1 year of age and ≥ 10 kg.
Treatment of reflux oesophagitis.
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease.
The posology recommendations are as follows:

Age	Weight	Posology
≥ 1 year of age	10-20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed.

Reflux oesophagitis: The treatment time is 4-8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease: The treatment time is 2–4 weeks.
Children and adolescents over 4 years of age.
Treatment of duodenal ulcer caused by H. pylori
The treatment should be supervised by a specialist.

The posology recommendations are as follows:

Weight	Posology
15–30 kg	Combination with two antibiotics: Omeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administrated together two times daily for one week.
31–40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated two times daily for one week.
> 40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated two times daily for one week.

Impaired renal function.
Dose adjustment is not needed in patients with impaired renal function.
Impaired hepatic function.
In patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient.
Elderly (> 65 years old).
Dose adjustment is not needed in the elderly.
Method of administration.
It is recommended to take Omarens capsules in the morning, preferably without food, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.
For patients with swallowing difficulties and for children who can drink or swallow semi-solid food.
Patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid e.g., fruit juice or applesauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water.
Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

Side-effects:
Blood and lymphatic system disorders: rare: leukopenia, thrombocytopenia; very rare: agranulocytosis, pancytopenia.
Immune system disorders: rare: hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock.
Metabolism and nutrition disorders: rare: hyponatraemia; not known: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia.
Psychiatric disorders: uncommon: insomnia; rare: agitation, confusion, depression; very rare: aggression, 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.
Gastrointestinal disorders: common: abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting; rare: dry mouth, stomatitis, gastrointestinal candidiasis; not known: Microscopic colitis.
Hepatobiliary disorders: uncommon: increased liver enzymes; rare: hepatitis with or without jaundice; very rare: hepatic failure, encephalopathy in patients with pre-existing liver disease.
Skin and subcutaneous tissue disorders: uncommon: dermatitis, pruritus, rash, urticaria; rare: alopecia, photosensitivity; very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN).
Musculoskeletal and connective tissue disorders: uncommon: fracture of the hip, wrist or spine; rare: arthralgia, myalgia; very rare: muscular weakness.
Renal and urinary disorders: rare: interstitial nephritis.
Reproductive system and breast disorders: very rare: gynaecomastia.
General disorders and administration site conditions: uncommon: malaise, peripheral oedema; rare: increased sweating.

Overdose:
There is limited information available on the effects of overdoses of omeprazole in humans. 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 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases. The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

Drug interactions:
Effects of omeprazole on the pharmacokinetics of other active substances.
Active substances with pH dependent absorption.
The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.
Nelfinavir, atazanavir.
The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole. Concomitant administration of omeprazole with nelfinavir is contraindicated.
Concomitant administration of omeprazole with atazanavir is not recommended.
Digoxin.
Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. 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 be then be reinforced.
Clopidogrel.
As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
Other active substances.
The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.
Active substances metabolised by CYP2C19.
Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.
Cilostazol.
Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.
Phenytoin.
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.*Unknown mechanism.*
Saquinavir.
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.
Tacrolimus.
Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.
Methotrexate.
When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.
Effects of other active substances on the pharmacokinetics of omeprazole.
Inhibitors CYP2C19 and/or CYP3A4.
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism.
Inducers of CYP2C19 and/or CYP3A4.
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

Cautions:
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.
Effects on ability to drive and use machines:
Omarens is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

Presentation:
Box with plastic bottle with 14 gastro-resistant capsules of 20 mg with instruction for use.

Storage:
Keep in dry place, protected from light at a temperature below 25°C.
Keep out of reach of children!

Shelf life:
Labeled. Do not use after expiry date.
Notice: After one month of the first opening of the plastic bottle, the remaining capsules should be thrown.

Distribution Condition:
Prescribed medicine.

SPEY
The holder of Trade Mark and Marketing Authorization is:
SPEY MEDICAL
England, UK
Manufactured by:
REPLEK FARM Ltd. Skopje
R. Macedonia