Bosch

For Medical Professional only

Omezol® Capsules

(Omeprazole)

اومیزول کیپسولز

(اومیپرازول)

DESCRIPTION:
The active ingredient in Omezol (omeprazole) capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42.

COMPOSITION:
Omezol Capsule 10mg
Each capsule contains:
Omeprazole U.S.P. 10mg
(As enteric coated pellets)
(Product Specs.: U.S.P.)

Omezol Capsule 20mg
Each capsule contains:
Omeprazole U.S.P. 20mg
(As enteric coated pellets)
(Product Specs.: U.S.P.)

Omezol Capsule 40mg
Each capsule contains:
Omeprazole U.S.P. 40mg
(As enteric coated pellets)
(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properties:
Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

Mechanism of Action:
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.

Pharmacokinetic Properties
Absorption:
Omeprazole are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. 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%.

Distribution:
The apparent volume of distribution is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Metabolism:
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 sulfone. 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.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called 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.

Elimination:
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 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 sulfone).
No metabolite has been found to have any effect on gastric acid secretion.

SPECIFIC POPULATIONS
Renal Insufficiency
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Hepatic Insufficiency
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.

Pediatrics:
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.

Elderly:
The metabolism rate of omeprazole is somewhat reduced in elderly.

THERAPEUTIC INDICATIONS:
Omezol capsules are indicated for in:
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

DOSAGE AND ADMINISTRATION:
Adults
Treatment of duodenal ulcers
The recommended dose in patients with an active duodenal ulcer is Omezol 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 Omezol 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 Omezol 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 Omezol 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 Omezol 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 Omezol 20 mg once daily. If needed the dose can be increased to Omezol 40 mg once daily.

H. pylori eradication in peptic ulcer disease
For the eradication of H. pylori the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.
- Omezol 20 mg + clarithromycin 500 mg + amoxicillin 1,000 mg, each twice daily for one week, or
- Omezol 20 mg + clarithromycin 250 mg (alternatively 500 mg) + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), each twice daily for one week or
- Omezol 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg (or 500 mg or tinidazole 500 mg), both three times a day for one week.

In each regimen, if the patient is still H. pylori positive, therapy may be repeated.

Treatment of NSAID-associated gastric and duodenal ulcers
For the treatment of NSAID-associated gastric and duodenal ulcers, the recommended dose is Omezol 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.

Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
For the prevention of NSAID-associated gastric ulcers or duodenal ulcers in patients at risk (age> 60, previous history of gastric and duodenal ulcers, previous history of upper GI bleeding) the recommended dose is Omezol 20 mg once daily.

Treatment of reflux oesophagitis
The recommended dose is Omezol 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 Omezol 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 Omezol 10 mg once daily. If needed, the dose can be increased to Omezol 20-40 mg once daily.

Treatment of symptomatic gastro-oesophageal reflux disease
The recommended dose is Omezol 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 Omezol 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 Omezol 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 Omezol 20-120 mg daily. When dose exceed Omezol 80 mg daily, the dose should be divided and given twice daily.

Paediatric population:
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. If symptom control has not been achieved after 2–4 weeks the patient should be investigated further.

Children and adolescents over 4 years of age
Treatment of duodenal ulcer caused by H. pylori
When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.

The posology recommendations are as follows:

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

Elderly:
Dose adjustment is not needed in the elderly

Patients with Hepatic Impairment:
In patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient.

Patients with Renal Impairment:
Dose adjustment is not needed in patients with impaired renal function.

Method of Administration:
It is recommended to take Omezol capsules in the morning, 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.

CONTRAINDICATIONS:
Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients. Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

WARNINGS AND PRECAUTIONS:
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. Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring. is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded. 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. Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. 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 PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), 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 by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections.
As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

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 Omezol. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.
Some children with chronic illnesses may require long-term treatment although it is not recommended.
As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

DRUG INTERACTIONS:
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. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition.
Concomitant administration of omeprazole with atazanavir is not recommended. Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

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
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. 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.

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.

Inhibitors of 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. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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.

ADVERSE EFFECTS:
Common:
Headache, Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)

Uncommon:
Insomnia, Dizziness, paraesthesia, somnolence, Vertigo, Increased liver enzymes, Dermatitis, pruritus, rash, urticaria, Fracture of the hip, wrist or spine, Malaise, peripheral oedema.

Rare:
Leukopenia, thrombocytopenia, Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock, Hyponatraemia, Agitation, confusion, depression, Taste disturbance, Blurred vision, Bronchospasm, Dry mouth, stomatitis, gastrointestinal candidiasis, Hepatitis with or without jaundice, Alopecia, photosensitivity, Arthralgia, myalgia, Interstitial nephritis, Increased sweating.

Very Rare:
Agranulocytosis, pancytopenia, Aggression, hallucinations, Hepatic failure, encephalopathy in patients with pre- existing liver disease, Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Muscular weakness, Gynaecomastia.

Not Known:
Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia, Hypomagnesaemia may also be associated with hypokalaemia, Microscopic colitis, Subacute cutaneous lupus erythematosus.

USE IN PREGNANCY AND LACTATION:
Pregnancy:
Omeprazole can be used during pregnancy.

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

OVERDOSE:
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.

SHELF LIFE:
3 years.

INSTRUCTIONS:
Protect from heat, sunlight & moisture, store below 30°C.
The expiration date refer to the product correctly stored at the required condition.
Keep out of the reach of children.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

PRESENTATION:
Omezol 10mg : Pack of 2x7's capsules in Alu Alu Blister Pack.
Omezol 20mg : Pack of 2x7's capsules in Alu Alu Blister Pack.
Omezol 40mg : Pack of 2x7's capsules in Alu Alu Blister Pack.

ہدایات :
دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف معتمد ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt) Ltd.
221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan