Size: 165x120mm

Revised
02-08-2023

OMEPRAZOLE

OBAX

40 mg Delayed Release Capsule

Proton Pump (H+K+ ATPase) Inhibitor

FORMULATION :
Each delayed release capsule contains:
Omeprazole.....40 mg
(As enteric coated pellets)

PRODUCT DESCRIPTION:
Dark blue/Light blue hard gelatin capsules containing white pellets.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors.
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.
Pharmacodynamic effects
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.
Effect on gastric acid secretion
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime 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% 24 hours after dosing.
Oral dosing with omeprazole 20 mg maintains an intragastric pH of ⩾ 3 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/normalizes acid exposure of the esophagus in patients with gastroesophageal reflux disease.
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.
No tachyphylaxis has been observed during treatment with omeprazole.
Effect on H. pylori
H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. *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* is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.
Eradication of *H. pylori* with omeprazole and antimicrobials is associated with high rates of healing and long-term remission of peptic ulcers.
Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.
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, which are benign and appear to be reversible.
Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.
An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

PHARMACOKINETICS :
Omeprazole is rapidly but variably absorbed after oral administration. Absorption is not affected by food. Omeprazole is acid-labile and pharmacokinetics may vary between the various formulations developed to improve oral bioavailability. The absorption of omeprazole also appears to be dose-dependent; increasing the dosage above 40 mg has been reported to increase the plasma concentrations in a non-linear fashion because of saturable first-pass hepatic metabolism. In addition, absorption is higher after long-term use.
Bioavailability of omeprazole may be increased in elderly patients, in some ethnic groups such as Chinese, and in patients with hepatic impairment, but is not markedly affected in patients with renal impairment.
Following absorption, omeprazole is almost completely metabolized in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19 to form hydroxyl-omeprazole, and to a small extent by CYP3A to form omeprazole, and to small extent by CYP3A to form omeprazole sulfone. The metabolites are inactive, and are excreted mostly in the urine and to a lesser extent in bile. The elimination half-life from plasma is reported to be about 0.5 to 3 hours. Omeprazole is about 95% bound to plasma proteins period.

INDICATIONS :
It is used in conditions where inhibition of gastric acid secretion may be beneficial, including aspiration syndromes, dyspepsia, gastroesophageal reflux disease, peptic ulcer disease, and the Zollinger-Ellison syndrome.

DOSAGE AND ADMINISTRATION :
Acid-Related Dyspepsia : 10-20 mg daily for 2-4 weeks.
Gastroesophageal Reflux Disease : 20 mg once daily for 4 weeks, followed by 4-8 weeks.
Children : Over 2 years, doses in the range 0.7 to 1.4 mg/kg daily, up to a maximum daily dose of 40 mg, have been given for 4 to 12 weeks.
Refractory Esophagitis : 40 mg daily. Esophagitis is 20 mg once daily, and for acid reflux is 10 mg daily.
Peptic Ulcer Disease : A single daily dose of 20 mg or 40 mg in severe cases.
Duodenal Ulcer : 8 weeks for gastric ulcer, 10 to 20 mg daily.
Zollinger-Ellison Syndrome: 60 mg once daily adjusted as required.
Or as prescribed by the physician.

CONTRAINDICATIONS :
Patients with known hypersensitivity to omeprazole.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Before giving omeprazole or other proton pump inhibitors to patients with gastric ulcers, the possibility of malignancy should be considered since these drugs may mask symptoms and delay diagnosis. Omeprazole and other proton pump inhibitors should be used with caution in hepatic impairment.

In the presence of any alarm symptoms (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 (H+ K+ ATPase) inhibitors is judged unavoidable, close clinical monitoring (e.g. virus load) 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.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump (H+ K+ ATPase) inhibitors 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 (H+ K+ ATPase) inhibitors treatment.
Some children with chronic illnesses may require long-term treatment although it is not recommended.
Omeprazole contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.
As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

PREGNANCY :
Proton pump inhibitors are not generally licensed for use during pregnancy, but a meta-analysis[1] of 5 studies of exposure to proton pump inhibitors during the first trimester, involving 593 exposed infants, found the relative risk of major abnormalities associated with such exposure to be only 1.18, with a 95% confidence interval ranging from 0.72 to 1.94. Meta-analysis of exposures to omeprazole (from 4 studies only) gave a relative risk of 1.05 (95% confidence interval 0.59 to 1.85). It was concluded that exposure to proton pump inhibitors, and omeprazole in particular, did not pose an important teratogenic risk. A retrospective epidemiological study of data from the Swedish Medical Birth Registry, which identified 955 exposed infants, also found no evidence of significant risk .

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

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. 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 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 by mouth 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%.

Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. 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 crossover 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.

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.

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.

Effects of other active substances on the pharmacokinetics of omeprazole
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.

OVERDOSE AND TREATMENT:
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.

ADVERSE DRUG REACTIONS:
Headache, diarrhea, and skin rashes; other effects include pruritus, dizziness, fatigue, constipation, nausea and vomiting, flatulence, abdominal pain, arthralgia and myalgia, urticaria, and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, angioedema, and anaphylaxis have been reported.
Effects on the CNS include occasional insomnia, somnolence, and vertigo; reversible confusional states, agitation, depression, and hallucination have occurred in severely ill patients. Raised liver enzymes, and isolated cases of hepatitis, jaundice, and hepatic encephalopathy, have been reported. Other adverse effects reported rarely or in isolated cases include paraesthesia, blurred vision, alopecia, stomatitis, sweating, taste disturbances, peripheral oedema, malaise, hyponatraemia, blood disorder (including agranulocytosis, Leukopenia, and thrombocytopenia), and interstitial nephritis.
Proton pump inhibitors may increase the risk of gastrointestinal infections because of their acid suppressive effects.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.
Keep all medicines out of children's reach.

AVAILABILITY:
Alu/Alu Blister Pack of 10's (Box of 30's)

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