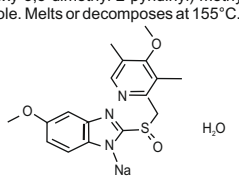
℞ OMEPRO

Omeprazole Powder for Solution
for Injection 40 mg/vial

OMEPRO (Omeprazole Powder for Solution for Injection 40 mg/vial)
Each vial contains Omeprazole Sodium 42.66 mg Equivalent to Omeprazole 40 mg.

DRUG DESCRIPTION

Omeprazole sodium is the S-isomer of Omeprazole. Omeprazole sodium is the salt form of a benzimidazole with selective and irreversible proton pump inhibitor activity. It is a weak base; unstable under acid conditions, but stable in alkaline media. The chemical designation is (R,S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl] - I H-benzimidazole. Melts or decomposes at 155°C.



Omeprazole sodium for Injection is supplied as a sterile, freeze-dried, white to off-white, crystaline, hygroscopic powder in a 10 mL vial.

Therapeutic indications
As alternative treatment of the oral formulation where fast and pronounced acidity inhibition is required for
Duodenal ulcer
Benign gastric ulcer
Reflux oesphagitis
Zollinger-Ellison syndrome

DOSAGE AND ADMINISTRATION

Dosage
Omeprazole 40mg as once daily intravenous application is recommended in those incidental cases where oral therapy is inappropriate and pronounced acidity inhibition is essential. The mean reduction of acid production in the stomach during 24hours is circa 90%.

With Zollinger-Ellison patients the recommended initial dosage is 60mg omeprazole per day. For a 60mg dose an additional half (5ml) of reconstituted solution should be given as an intravenous injection. Any unused solution should be discarded. Higher dosage can be necessary and the dosage of more than 60mg per day the administration of the daily dosage should be spread out the day.

A one week treatment is usually sufficient.

Administration

Omeprazole sodium for injection is for intravenous administration only and must not be given by any other route.

Direction for reconstitution

Omeprazole sodium for injection should only be dissolved in water for injection. After reconstitution outside validated aseptic conditions, use within 4 hours of preparation and any unused portion should be discarded. The duration of administration should be over 5 minutes.

Use in the elderly

Dosage adjustment is not necessary.

Use in children

There is limited experience of use in children. Therefore omeprazole injection is not recommended in children.

Impaired renal function

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

Impaired hepatic function

As half-life is increased in patients with impaired hepatic function, the dose requires adjustment and a daily dose of 10-20 mg may be sufficient.

CONTRAINDICATIONS

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients. Omeprazole like other proton pump inhibitors (PPIs) should not be used concomitantly with nelfinavir (See section Drug Interactions).

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 (see section Contraindications). 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 (see section Warnings and Precautions). 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
In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

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
Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted (see section Warnings and Precautions).

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.

WARNINGS AND PRECAUTIONS

Hypomagnesaemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Subacute cutaneous lupus erythematosus (SCLE)

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving omeprazole sodium, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Clostridium difficile-associated diarrhoea

Published observational studies suggest that proton pump inhibitor (PPI) therapy like omeprazole sodium may be associated with an increased risk of Clostridium difficileassociated diarrhoea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (see Side Effects). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines (see Dosage and Administration and Side Effects).

Concomitant use of Omeprazole sodium with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients (see Drug Interactions).

In the presence of any alarm symptoms (eg, 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 (See section Drug Interactions). If the combination of atazanavir with a proton pump inhibitor 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 (see section Drug Interactions). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter, and in hospitalized patients,

Leaflet size: 140 x 400 mm

Non - printing Colour :
Die Cut

Printing Colour :
Black

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.

The total amount of sodium (Na+) in the reconstituted solution is less than 1 mmol (23 mg) per 40 mg dose.

PREGNANCY AND LACTATION

Pregnancy and lactation Use in pregnancy

The analysis of the results from three epidemiological studies has revealed no evidence of adverse events of Omeprazole sodium on pregnancy or on the health of the fetus/newborn child. Omeprazole sodium for injection can be used during pregnancy.

Use in lactation

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

SIDE EFFECTS

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

SOC/frequency	Adverse reaction
Blood and lymphatic system disorders	
Rare:	Leukopenia, thrombocytopenia
Very rare	Agranulocytosis, pancytopenia
Immune system disorders	
Rare	Hypersensitivity reaction e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	
Rare	Hyponatraemia
Very rare	Hypomagnesaemia (see section Warning and Precautions). 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
Very rare	Dyspepsia
Not Known	Microscopic colitis Clostridium difficile-associated diarrhoea (CDAD)
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, Steven-Johnsonsyndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Uncommon	Fracture of the hip, wrist or spine (see section Warning and Precautions).
Rare	Arthralgia, myalgia
Very rare	Muscular weakness
Not Known	Fractures
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

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole intravenous injection, especially at high doses, but no causal relationship has been established.

Postmarketing experience

Immune system: systemic lupus erythematosus
Skin and subcutaneous tissue: cutaneous lupus erythematosus

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.

Intravenous doses of up to 270 mg on a single day and up to 650 mg over a three-day period have been given in clinical trials without any dose-related Adverse effects.

CLINICAL PHARMACOLOGY

ATC-code: A02B-C01

Pharmacotherapeutic group: Drug for peptic ulcer and gastro-oesphageal reflux disease (GORD), Proton pump inhibitors

Omeprazole, a substituted benzimidazole, is a gastric proton pump inhibitor, i.e. omeprazole directly and dose-dependently inhibits enzymes H+, K+-ATPase, which is responsible for the gastric acid secretion in the gastric parietal cells. Due to this selective intracellular mode of action and the low affinity for other membrane-bound receptors (such as the histamine H2, muscarine M1 or gastrinergic receptors), omeprazole has been assigned to a separate class of acid-inhibiting agents, which blocks the final step of acid production.

As a consequence of its mode of action, omeprazole leads to an inhibition of both basal and stimulable acid secretion, irrespective of the stimulus type.

Thus, omeprazole increases the pH-value and reduces the volume of gastric acid secretion.

As a week base the prodrug omeprazole accumulates in the acid environment of the parietal cells and will only be effective as an inhibitor of the H+, K+-ATPase after being protonised and rearranged.

In an acid environment, at a pH of less than 4 the protonised omeprazole is converted to omeprazole sulphenamide, the active substance proper.

Compared to the plasma half-life of the omeprazole base, omeprazole sulphenamide remains in the cell for a longer period of time. Thus the duration of the inhibition of acid secretion is substantially longer then the period in which omeprazole- base is present in plasma. The degree of inhibition of acid secretion is directly correlated to the area under the plasma concentration-time curve (AUC) but not to the plasma concentration at any given time, a sufficiently low pH- value is only found in the gastric parietal cells; this explains the high specificity of omeprazole. It is the omeprazole-sulphenamide that binds to the enzyme and inhibits its activity.

If the enzyme- system is inhibited, the pH value increases and less omeprazole accumulates or is converted in the gastric parietal cells. Consequently, the accumulation of omeprazole is regulated by a kind of feedback-mechanism.

Intravenous administration of omeprazole affords a quick and effecting inhibition of gastric acid production. With duodenal ulcer patients the mean reduction of basal and stimulated acid production during 24hour is circa 90%.

A single intravenous injection of 40mg has, over a period of 24 hour, almost the same effect on acid production as an oral dose of 80mg.

Pharmacokinetics

Distribution
The distribution volume of omeprazole in the body is relatively small (0.3l/kg of body weight) and corresponds to that of the extracellular fluid. Approximately 95% is protein bound.

Metabolism and excretion
Omeprazole is entirely metabolised, mainly in the liver by CYP 2C19 enzyme. The half-life is about 40minutes, and the total plasma clearance is 0.3 to 0.6l/min.

A small percentage of het patients lack a functional CYP2C19 and have reduced elimination rate of omeprazole. In these cases, the terminal elimination half-life can be approximately 3 times as long as the normal value, and the area under the plasma concentration- time curve (AUC) of orally administered Omeprazole can increase by up to 10 times. The sulphone, sulphide and hydroxy-omeprazole are found in plasma. These metabolites have no significant effect on acid secretion.

About 20% of administered dose is excreted in faeces and remaining 80% is excreted in urine as metabolites. The two major urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

Special patient populations

In patients with renal impairment, the systemic availability of omeprazole was very similar to that in healthy subjects.

In patients with chronic hepatic disease the clearance of omeprazole is reduced, and the plasma half-life can increase up to approximately 3hours. The systemic bioavailability can be enhanced in these patients.

The bioavailability of omeprazole is slightly elevated in the elderly, and the elimination rate is slightly diminished. But the individual values are nearly equal to that of the young healthy subjects and there is no indication that the tolerance in the elderly patients treated with normal dose of omeprazole is reduced.

After intravenous administration of 40mg omeprazole for 5 days, the absolute measured bioavailability increased about 50%; this can be explained by decreased hepatic clearance due to saturation of the CYP2C19 enzyme.

Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole or subjected to partial fundectomy. These changes are the results of sustained hypergastrinaemia secondary to acid inhibition.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Omeprazole sodium powder for solution for injection must not be mixed with other medicinal products, except that mentioned in section TO RECONSTITUTE. The reconstituted products must not be mixed with other medicinal products.

Special precautions for disposal and other handling

The entire contents of the vial should be completely dissolved with 10ml of sterile water for Injection. Use on one patient during one treatment only.

Do not use if any particulate matter are present in the reconstituted solution.

HOW SUPPLIED

OMEPRO (Omeprazole Powder for Solution for Injection 40 mg/vial)

Each vial contains Omeprazole Sodium 42.66 mg Equivalent to Omeprazole 40 mg.

White to pale yellow lyophilized cake (or) powder in 10 mL Type-I amber color moulded glass vial with 20 mm grey bromo butyl rubber stopper and 20 mm red color flip off aluminium seal.

PACKAGING INFORMATION:

Omeprazole sodium for Injection is available in sterile single-use vials individually packed in a carton.

TO RECONSTITUTE:

Add 10 mL of Water for injection to make a solution containing 4 mg/mL. Shake to dissolve. Administer solution within 4 hours. Discard unused portion. Store at or below 25°C.

Excipients
Sodium Carbonate Anhydrous

PACK STYLE:

10 mL amber color moulded glass vial.

STORAGE:

Store below 30°C and protect from light.
Product Owner:
HETERO LABS LIMITED
7-2-A 2, Hetero Corporate,
Industrial Estates, Sanath nagar,
Hyderabad - 500 018, INDIA.

Manufactured by:
Aspiro
ASPIRO PHARMA LIMITED
Survey No. 321, Biotech Park,
Phase-III, Karkapatla Village,
Markook Mandal, Siddipet Dist.,
Telangana State- 502281, INDIA

2xxxxxx