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R OMEPRO
(Omeprazole Sodium
Powder for Solution
for Injection 40mg/Vial)

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Name of Active ingredient
Omeprazole 40mg/vial (as Omeprazole sodium)

Excipients
Sodium carbonate, water for injection.

Dosage form
Powder for Solution for Injection

Product Description
A white to pale yellow lyophilized cake (or) powder in 10 mL Type-I, amber color moulded glass vial with 20 mm grey bromobutyl rubber stopper and 20 mm red color flip off aluminium seal. The reconstituted solution is clear and colour less.

Pharmacodynamics/Pharmacokinetics
Pharmacodynamics
Pharmacotherapeutic group: 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.

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

Effect on gastric acid secretion
Intravenous omeprazole produces a dose dependent inhibition of gastric acid secretion in humans. In order to immediately achieve a similar reduction of intragastric acidity as after repeated dosing with 20 mg orally, a first dose of 40 mg intravenously is recommended. This results in an immediate decrease in intragastric acidity and a mean decrease over 24 hours of approximately 90% for both IV injection and IV infusion.

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.

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 slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

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

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

Biotransformation
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.

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
Total plasma clearance is about 30-40 l/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of a dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-linearity
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).

Indications
OMEPRO Injection is indicated for the treatment of the following conditions:

- Duodenal ulcer
- Gastric ulcer
- Reflux oesophagitis
- Zollinger-Ellison syndrome

Recommended dose
OMEPRO Injection is administered to patients who are unable to take oral therapy or in patients before surgery. It is administered only by specialized personnel.
OMEPRO is administered by slow intravenous injection in a dose of 40mg over a minimum period of 2 ½ minutes once daily. Intravenous administration achieves immediate reduction of gastric

acidity with a mean decrease over 24 hours of approximately 90%.
In patients with Zollinger-Ellison syndrome the recommended initial dosage of OMEPRO injection is 60 mg once daily. Higher daily doses may be required and the dose should be divided and given twice daily.

For the preparation of OMEPRO solution for injection, only water for injection should be used. No other solvents could be used. After reconstitution, intravenous injection should be administered slowly over a period of at least 2 ½ minutes to a maximum rate of 4ml per minute. Solution should be used within 4 hours of reconstitution.

Prevention of gastric acid aspiration
In case intravenous administration is preferred for the prevention of gastric acid aspiration, OMEPRO Injection should be administered 1 hour before operation. If operation is set back for more than 2 hours, another injection should be administered.

Renal Impairment
Dosage adjustment is not required in patients with impaired renal function.

Hepatic Impairment
Bioavailability and half-life of omeprazole in plasma are increased in patients with hepatic impairment, therefore a daily dose of 20mg is usually sufficient.

Children
Safety and efficacy of omeprazole has not been demonstrated in children.

Elderly
Dosage adjustment is not required in elderly patients.

Mode of administration
Injection

Contraindications
Known 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.

Warnings and precautions
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 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 with 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.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Regular Surveillance
Patients on proton pump inhibitor treatment (particularly those treated for long term) 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 Omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with 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), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Fracture
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.

Clostridium Difficile Diarrhea
Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

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.

Interaction with other Medicaments

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
Concomitant administration of omeprazole with nelfinavir is contraindicated. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure and the mean exposure of the pharmacologically active metabolite M8 was reduced. 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 resulted in a 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 resulted in a decrease of atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin
Concomitant treatment with omeprazole (20 mg daily) and digoxin increased the bioavailability of digoxin. 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 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 and a decreased maximum inhibition of (ADP induced) platelet aggregation. 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

Size : 200 x 380 mm
Colour : Black
Note: Pharma code position and Orientation are tentative, will be changed based on folding size.

Space for
Pharma Code

2xxxxxx
⌘ OMEPRO
(Omeprazole Sodium
Powder for Solution
for Injection 40mg/Vial)

Omeprazole given in doses of 40 mg increased Cmax and AUC for cimetastazol and one of its active metabolites.

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 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 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.

Pregnancy and lactation

Pregnancy

Omeprazole can be used during pregnancy.

Breastfeeding

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

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

Side effects

Summary of the safety profile

The most common side effects are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC).

System Organ Class	Frequency	Undesirable Effect
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 can correlate with
		hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
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, fundic gland polyps (benign)
	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)
	Not known	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
	Not known	Subacute cutaneous lupus erythematosus
Renal and urinary disorders	Rare	Interstitial nephritis
	Very rare	Gynaecomastia
General disorders and administration site conditions	Uncommon	Malaise, increased sweating
	Rare	Increased sweating
Infections & Infestations		Clostridium difficile associated diarrhoea
Metabolic/Nutritional		Vitamin B12 deficiency

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.

Symptoms and treatment of 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 reactions.

Effects on ability to drive and use machines

Omeprazole 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.

Instructions for Use

Omeprazole for injection is single dose vial. For IV injection – Vial must be reconstituted with 10 ml water for injection. After addition of water for injection, shake the vial till all drug get dissolved completely. The resultant solution concentration is 4 mg/ml of omeprazole solution should be given slowly (over a period of 5 minutes) as an Intravenous injection. After reconstitution solution should be used immediately or within 4 Hours and any unused portion should be discarded.

"It is recommended to use bevelled sterile transfer needle that is 21 gauge or smaller in diameter".

Incompatibilities

No other drugs should be mixed with reconstituted Omeprazole powder for solution for infusion.

Storage condition

Store below 30 C and protect from moisture.

After dilution: Up to 4 hours when stored at room temperature (below 25 C)

Shelf life: 24 months. After dilution: Up to 4 hours when stored at room temperature (below 25 C).

Packaging available

Amber, Type I glass 10ml vials with rubber stopper and aluminium flip-off.

Each carton contains 1 vial.

Name and address of Manufacturer

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Name and address of Product Registration Holder

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