omepiva

40MG POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

COMPOSITION
Each vial contains Omeprazole Sodium 42.55mg equivalent to Omeprazole 40mg.

DESCRIPTION
Powder
Before Reconstitute: Hygroscopic, white to off-white solid.
After reconstitute: A clear, colourless or pale yellowish-brown solution.

Solvent
A clear and colourless solution

The powder for solution substance is hygroscopic white to off-white solid packed in clear glass vial of 10 ml. Each ampoule contains 10 ml of solvent for reconstitution. The solvent is slightly viscous solution containing citric acid monohydrate and polyethylene glycol 400.

PHARMACODYNAMICS
Pharmacotherapeutic group: Proton pump inhibitors. ATC code: A02BC01

Mechanism of action
Omeprazole, a racemix 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-dependant and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamics effect
All pharmacodynamics effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion
Intravenous omeprazole produces a dose dependant 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 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 diseases. *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 treatment with anti-secretory drugs, serum gastrin will increase due to decrease acid secretion. Also chromogranin A (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.

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 count 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 *Clotridium difficile.*

PHARMACOKINETICS
Distribution
The apparent volume of distribution in healthy person 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 the 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. 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 elimination of omeprazole is unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects of age 75-79 years old.

INDICATION
omepiva injection is indicated for alternative use to oral medication in

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

RECOMMENDED DOSAGE
Duodenal ulcer, gastric ulcer and reflux oesophagitis: patients who cannot be given oral medication can be treated parenterally with 40mg once daily. The usual treatment period before transfer to oral treatment is 2 - 3 days.

In patients with Zollinger-Ellison syndrome the recommended initial dosage of Zefxon injection is 60 mg once daily. Higher daily doses may be required and the dose should be divided and given twice daily. In Zollinger-Ellison syndrome the dose should be adjusted accordingly to individual.

Intravenous treatment can be given as injection, whereby the solution for injection must be given slowly over a period of at least 2 1/2 minutes and with a rate of maximum 4ml per minute.

Impaired renal function
A dose adjustment is not necessary for patients with impaired renal function.

Impaired liver function
In patients with impaired liver function clearance is greatly reduced.

Elderly patients
Dose adjustment is not necessary in elderly patients.

Children
There is only limited experience of treatment in children

ROUTE OF ADMINISTRATION
IV treatment can be given as injection, whereby the solution for injection must be given slowly over a period of at least 2 1/2 minutes and with a rate of maximum 4 mL per minute.

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.

WARNINGS / 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 all acid blocking medicines, may reduce the absorption vitamin B_{12} (cyanocobalamin) due to hypo-or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} 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* and, in hospitalized patients, possibly also *Clostridium difficile*.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors like omepiva Injection 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 proton pump inhibitor.

For patients expected to be on prolonged treatment or who take proton pump inhibitors with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting proton pump inhibitor 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. 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 omepiva injection. 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.

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

This medicinal product is essentially 'sodium-free'. The total amount of sodium (Na+) in the reconstituted solution is less than 1 mmol (23 mg) per 40 mg dose.

Regular Surveillance
Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

Clostridium Difficile Diarrhea
It is suggested that PPI therapy may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in 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.

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
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 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 300mg/ritonavir 100 mg resulted in a decrease of the atazanavir exposure. Increasing the atazanavir dose by 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400mg/ ritonavir 100 mg resulted in decrease in the atazanavir exposure as compared to atazanavir 300mg/ ritonavir 100 mg once daily.

Digoxin
Concomitant treatment of omeprazole (20 mg daily) with 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
The pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e., four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation.

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 such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol
Omeprazole increased C_{max} and AUC for cilostazol 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.

Warfarin or other vitamin K antagonists
In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary.

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.

Incompatibilities
This medicinal product should not be mixed with other medicinal products than those mentioned in "Instructions for Use".

PREGNANCY AND LACTATION

Pregnancy
No adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child has been reported. 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Omeprazole is not likely to affect the ability to drive or use machines. Adverse reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

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

Other possible side effects include *Clostridium difficile* associated diarrhoea and vitamin B12 deficiency.

Blood and lymphatic system disorders
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis and pancytopenia.

Ear and labyrinth disorders
Uncommon: Vertigo.

Eye disorders
Rare: Blurred vision.

Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign).
Rare: Dry mouth, stomatitis, gastrointestinal candidiasis.
Not known: Microscopic colitis

General disorders and administration site conditions
Uncommon: Malaise, peripheral oedema
Rare: Increased sweating

Hepatobiliary disorders
Uncommon: Increased liver enzymes Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease.

Immune system disorders
Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Infections & infestations
Clostridium difficile associated diarrhea.

Metabolism and nutrition disorders
Rare: Hyponatraemia
Not known: Hypomagnesaemia
Vitamin B12 deficiency

Musculoskeletal and connective tissue disorders
Uncommon: Fracture of the hip, wrist or spine Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance.

Psychiatric disorders
Uncommon: Insomnia
Rare: Agitation, confusion, depression
Very rare: Aggression and hallucinations

Renal and urinary disorders
Rare: Interstitial nephritis.

Reproductive system and breast disorders Very rare: Gynaecomastia.

Respiratory, thoracic and mediastinal disorders Rare: Bronchospasm

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).
Not known: Subacute cutaneous lupus erythematosus

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.

SYMPTOM & 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.

STORAGE CONDITION
Store below 30ºC.
Protect from light.
Retain in carton until time of use.

The solution will remain stable for 4 hours below 30ºC after reconstitution. From a microbiological point of view the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

Any unused portion should be discarded.

INSTRUCTIONS FOR USE
Solution for injection is obtained by dissolving the sterile dry substance with 10ml of solvent. No other solvent may be used. The reconstituted solution for injection must be used within 4hours.

The stability of omeprazole is influenced by the pH of the solution for injection, which is why no other solvents or quantities should be used for dilution. Improperly prepared solutions can be identified by their yellow to brown discolouration and must not be used. Use only clear, colourless or pale yellowish-brown solutions.

Preparation
NOTE: Steps 1 to 5 must be performed in immediate sequence:
1. With a syringe draw all of the solvent from the ampoule (10ml)
2. Add approximately 5ml of the solvent to the vial with freeze-dried omeprazole.
3. Withdraw as much air as possible from the vial back into the syringe. This will make it easier to add the remaining solvent.
4. Add the remaining solvent into the vial and make sure that the syringe is empty.
5. Rotate and shake the vial to ensure all the freeze-dried omeprazole has dissolved.

omepiva Injection must be given only as an intravenous injection and it must not be added to infusion solutions. After reconstitution the injection should be given slowly over a period of at least 2.5 minutes at a maximum rate of 4 ml per minute.

Any unused product or waste material should be disposed of in accordance with local requirements.

SHELF LIFE
2 years

The solution will remain stable for 4 hours below 30ºC after reconstitution. From a microbiological point of view the product should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions.

Any unused portion should be discarded.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Powder and Solvent for Solution for Injection.
1 x 10ml vial (clear glass) of 40mg Powder for Solution and 1 x 10ml ampoule (clear glass) of Solvent for Solution for Injection

PRODUCT REGISTRATION HOLDER /MANUFACTURER
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