OMEZOL LYO-INJECTION

DESCRIPTION
It occurs as a white to off-white lyophilization powder in vial.

NAME AND STRENGTH OF ACTIVE INGREDIENT
Each vial contains 42.6 mg Omeprazole Sodium equivalent to Omeprazole……40 mg.

MECHANISMS OF ACTION
Omeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+/K^+-ATPase proton pump in the parietal cell.

SUMMARY OF PHARMACOKINETICS
Omeprazole Sodium is absorbed rapidly. Omeprazole Sodium is 95% bound to plasma proteins. It is entirely metabolized, mainly in the liver, about 80% of the metabolites are excreted in urine and the remainder in feces.

PHARMACODYNAMICS
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased 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 (PPIs) 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.

TOXICOLOGY (BRIEF)
To date there has been no experience with deliberate overdosage, nor has there been any indication that it has acute toxic effects in human.

INDICATIONS
Alternative therapy for the following conditions which cannot be treated effectively with oral medication: duodenal ulcer, gastric ulcer, ulcerative oesophagitis and Zollinger-Ellison syndrome.

CONTRAINDICATIONS
Omeprazole is contraindicated in patients with known hypersensitivity to the drug or any ingredient in the formulation.

SIDE EFFECTS AND ADVERSE REACTIONS
It is generally well tolerated and adverse reactions have generally been mild and reversible. The following have been reported as adverse events in clinical trials or reported from routine use but in many cases a relationship to treatment with omeprazole has not been established.

Skin rash, urticaria and pruritus have been reported, usually resolving after discontinuation of treatment. In addition, photosensitivity, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema and alopecia have been reported in isolated cases.

Diarrhea and headache have been reported and may be severe enough to require discontinuation of therapy in a small number of patients. In the majority of cases, the symptoms resolved after discontinuation of therapy.

Other gastrointestinal reactions include constipation, nausea/vomiting, flatulence and abdominal pain. Dry mouth, stomatitis and candidiasis have been reported as isolated cases.

Paraesthesia has been reported. Dizziness, light-headedness and feeling faint have been associated with treatment, but all usually resolve on cessation of therapy. Somnolence, insomnia and vertigo have been reported rarely. Reversible mental confusion, agitation, depression and hallucinations have occurred predominantly in severely ill patients.

Arthritic and myalgic symptoms have been reported and have usually resolved when therapy is stopped.

In isolated cases, the following have been reported: blurred vision, taste disturbance, aggression, peripheral oedema, hyponatraemia, increased sweating, gynaecomastia, impotence, leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, anaphylactic shock, malaise, fever, bronchospasm, encephalopathy in patients with pre-existing severe liver disease, hepatitis with or without jaundice, rarely hepatic failure and interstitial nephritis which has resulted in acute renal failure.

Isolated cases of irreversible visual impairment have been reported in critically ill patients who have received the product, particularly at high doses, however no causal relationship has been established.

Increase in liver enzymes has been observed rarely.

Subacute Cutaneous Lupus Erythematosus (SCLE)
Skin and subcutaneous tissue disorders
Frequency “not known”: Subacute cutaneous lupus erythematosus

Interstitial Nephritis
Renal and urinary disorders: Interstitial nephritis

Hypomagnesaemia
Metabolism and nutritional disorders
Frequency “not known”: Hypomagnesaemia

Fracture
Musculoskeletal disorders
Frequency “uncommon”: Fracture of the hip, wrist or spine

***Clostridium difficile* Diarrhea**
Infections and Infestations: *Clostridium difficile*-associated diarrhea (CDAD)

Fundic Gland Polyps (Benign)
Gastrointestinal disorders
Frequency “common”: Fundic gland polyps (benign)

Vitamin B12 Deficiency
Metabolic/Nutritional: Vitamin B12 deficiency

PRECAUTIONS AND WARNINGS
(1) Before giving omeprazole to patients with gastric ulcers, the possibility of malignancy should be excluded since omeprazole may mask symptoms and delay diagnosis.

(2) Omeprazole inhibits the metabolism of some drugs metabolized by the hepatic cytochrome P-450 enzyme system and may increase plasma concentrations of diazepam, phenytoin, and warfarin.

(3) Impaired hepatic function
Patients with impaired hepatic function show a markedly increased bioavailability, a reduced total plasma clearance and up to a four-fold prolongation of the elimination half-life. However urinary recovery over 96 hours remains unchanged, indicating no accumulation of omeprazole or its metabolites. A daily dose of 10-20 mg may be sufficient for patients with impaired hepatic disease.

(4) Use in pregnancy
There are no adequate or well-controlled studies in pregnant women. Omeprazole should only be given to pregnant women if its use is considered essential.

(5) Use in lactation
Although omeprazole is excreted at low concentrations in the milk of lactating female rats, it is not known if omeprazole or its metabolites appear in human breast milk. Therefore it is recommended that omeprazole not be used during breast-feeding.

(6) 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 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 PPIs.

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), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

(7) *Clostridium difficile-associated* diarrhea
Published observational studies suggest that PPI therapy like omeprazole may be associated with an increased risk of *Clostridium difficile-associated* diarrhea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhea that does not improve (see SIDE EFFECTS AND ADVERSE REACTIONS). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

(8) Bone fracture

Several published observational studies suggest that PPI therapy may be associated with an increased overall 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), predominantly in the elderly or in presence of other recognized risk factors. 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 and they should have an adequate intake of Vitamin D and calcium (see RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION and SIDE EFFECTS AND ADVERSE REACTIONS).

(9) Concomitant use of omeprazole 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 Interaction).

(10) Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE)
CLE and 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. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Omezol Lyo Injection 40 mg. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPI. 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 Omezol Lyo-Injection, 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.

(11) Interference with laboratory tests
Increased CgA level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, Omezol Lyo Injection 40 mg treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see PHARMACODYNAMICS). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of PPI treatment.

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

(13) 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.

Drug interaction:
Food: Concomitant administration of food has no effect on the bioavailability of omeprazole, but its rate of absorption may be reduced.

Drugs: Omeprazole is metabolized via the hepatic cytochrome P450 system and may be expected to interact with the pharmacokinetics of other drugs metabolized by this system. The absence of an interaction with either theophylline or propranolol suggests that omeprazole interacts with only a limited number of drugs metabolized by the cytochrome P450 system. Of the drugs studied to date, omeprazole has only demonstrated an interaction with diazepam, phenytoin and warfarin.

Diazepam: Following repeated oral dosing of omeprazole 40 mg once daily the mean elimination half-life of diazepam was increased 130% with a consequent significant increase in plasma diazepam concentrations. Consideration should be given to a reduction in diazepam dosage when omeprazole is co-prescribed.

Phenytoin: Oral omeprazole 40 mg daily for seven days reduced plasma clearance of intravenous phenytoin and increased the elimination half-life by 27%. It is recommended that the plasma concentration of phenytoin be monitored in patients co-prescribed omeprazole and phenytoin.

Warfarin: Concomitant administration of oral omeprazole 20 mg to healthy volunteers caused a slight though statistically significant increase in the plasma concentration of the R-enantiomer of warfarin.

Plasma concentrations of the more potent S-enantiomer were not affected. A small but statistically significant increase in warfarin's anticoagulant activity accompanied this stereoselective interaction. It is recommended that coagulation tests be monitored closely when initiating or ceasing omeprazole in patients co-prescribed warfarin.

Ketoconazole: The absorption of some drugs might be altered due to the decreased intra-gastric acidity. Therefore it can be predicted that the absorption of ketoconazole will decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

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 PRECAUTIONS AND WARNINGS).

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION

(1) Omeprazole intravenous should only be used where oral medication is inappropriate, e.g. in severely ill patients. Dose: 40 mg once daily.

(2) The dose used in the treatment of Zollinger-Ellison syndrome should be adjusted according to individual response.

(3) Dilute OMEZOL Lyo-Injection with 10 mL solvent (10 mL/Amp.), and no other infusion solution should be used. Discolouration may occur if incorrect reconstitution technique is used. Inject over a period of not less than 2.5 minutes. Inject at a rate no greater than 4 mL/min.

Instruction for reconstitution

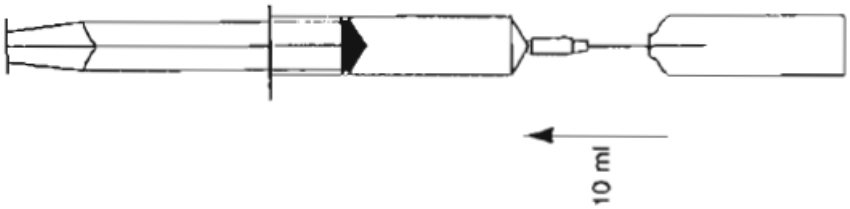
The Omezol Lyo-Injection 40 mg solution is reconstituted through dissolving the freeze-dried substance in 10 mL of the enclosed solvent.

Stability of omeprazole is pH dependent and to ensure stability of the reconstituted product 10 mL of the enclosed solvent shall be used.

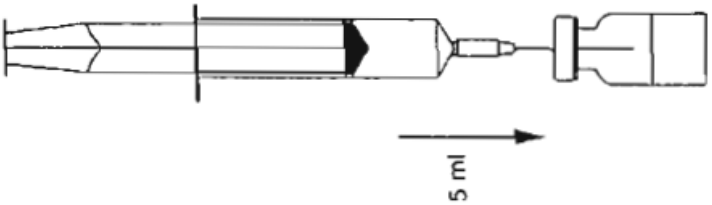
Preparation

NOTE: Stages 1 to 5 shall be done in immediate sequence

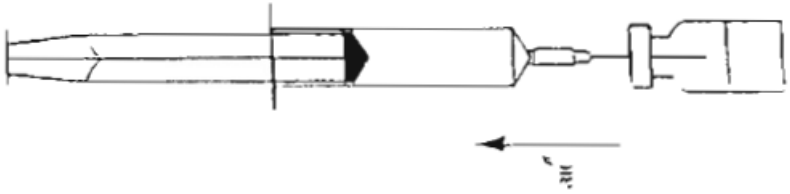
1. With a new syringe draw 10 mL of solvent from the ampoule.



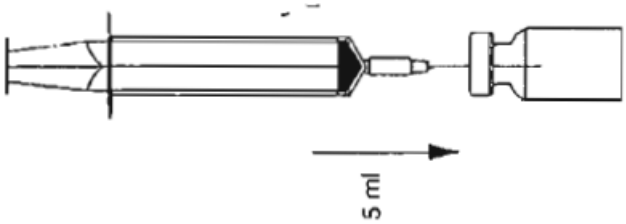
2. Slowly add approximately 5 mL of the solvent into the vial with the freeze-dried omeprazole.



3. Withdraw as much air as possible from the vial back into the syringe in order to reduce positive pressure. This will make it easier to add the remaining solvent.



4. Add the remaining solvent into the vial, make sure that the syringe in empty.



5. Rotate and shake the vial to ensure adequate mixing of omeprazole and solvent.

(4) Keep reconstituted solution below 25°C and use within 4 hours.

(5) The appearance of the final product shows colorless or pale yellow after reconstitution with its solvent.

(6) No dosage adjustment of OMEZOL Lyo-Injection is necessary in the impaired renal function and elderly patients. There is no experience with OMEZOL Lyo-Injection in children.

SYMPTOMS AND TREATMENT FOR OVERDOSAGE AND ANTIDOTE(S)
To date there has been no experience with deliberate overdosage, nor has there been any indication that OMEZOL Lyo-Injection has acute toxic effects in human.

As in all cases where overdosing is suspected, treatment should be supportive and symptomatic.

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

PACKING AND PACK SIZES
1 vial + 1 ampoule of solvent in a box.

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS
Store below 25°C. Protect from light.
Refer to product carton and labels for expiry date.
Keep reconstituted solution below 25°C and use within 4 hours.

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