NEW ZEALAND DATA SHEET

OMEZOL IV

1. Product Name

Omezol IV, 40 mg, powder for infusion.

2. Qualitative and Quantitative Composition

Each vial contains 40 mg of omeprazole lyophilised powder.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Each glass vial contains a white lyophilised powder consisting of omeprazole 40 mg, which is intended to be reconstituted.

4. Clinical Particulars

4.1 Therapeutic indications

Omezol IV is indicated primarily for the treatment of Zollinger-Ellison syndrome, and may also be used for the treatment of gastric ulcer, duodenal ulcer and reflux oesophagitis.

4.2 Dose and method of administration

Dose

In patients with duodenal ulcer, gastric ulcer or reflux oesophagitis where oral medication is inappropriate, Omezol IV 40 mg once daily is recommended. In patients with Zollinger-Ellison syndrome the recommended initial dose of omeprazole given intravenously is 60 mg daily. Higher daily doses may be required and the dose should be adjusted individually. When doses exceed 60 mg daily, the dose should be divided and given twice daily.

Special populations

Elderly

Dose adjustment is not needed in the elderly.

Renal impairment

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

Hepatic impairment

As plasma half-life of omeprazole is increased in patients with impaired hepatic function a daily dose of 10 - 20 mg may be sufficient.

Paediatric

There is limited experience with intravenous omeprazole in children.

Method of administration

Omezol IV infusion 40 mg should be given as an intravenous infusion (over a period of 20 - 30 minutes or more). The contents of one vial must be reconstituted with 5 mL of saline or 5 mL of 5% dextrose, then further diluted to 100 mL with saline for infusion or 5% dextrose for infusion. No other infusion solution should be used.

The solution should be used within 12 hours when omeprazole is dissolved in saline and within 6 hours when dissolved in 5% dextrose. After reconstitution, start the infusion immediately. The constituted solution should not be mixed or co-administered in the same infusion set with any other drug.

4.3 Contraindications

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, the possibility of malignancy should be excluded as treatment may alleviate symptoms and delay diagnosis.

Hypomagnesaemia

Hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) medication for at least three months, and in most cases for a year. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia.

Severe hypomagnesaemia may result in serious adverse events such as dizziness, fatigue, delirium, tetany, seizures, and potentially also arrhythmias.

In some patients, treatment of hypomagnesaemia with magnesium replacement was not sufficient to correct the magnesium imbalance and discontinuation of the PPI was required. In patients later retreated with the same or different PPI, hypomagnesaemia returned within a shorter time period.

For patients expected to be on prolonged treatment or who take PPIs with other medicines such as digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), consideration should be given to monitoring magnesium levels prior to initiation and periodically thereafter.

4.5 Interaction with other medicines and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other medicines

Nelfinavir, atazanavir

Omeprazole has been reported to interact with some antiretroviral medicines. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicine. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Concomitant administration with omeprazole and medicines such as atazanavir and nelfinavir is therefore not recommended.

Citalopram, escitalopram

Co-administration of omeprazole (20 mg) with citalopram (20 mg single dose) doubles the AUC of the S-isomer of citalopram, but the R-isomer of citalopram is not affected. A reduction in the dose of

citalopram may be necessary based on clinical judgement. For patients taking omeprazole, the citalopram dose should not exceed the maximum dose of 20 mg/day.

Co-administration of omeprazole (30 mg) with escitalopram (20 mg single dose) increased the plasma levels (approximately 50%) and terminal half-life (31%) of escitalopram. A reduction in the dose of escitalopram may be necessary based on clinical judgement.

Digoxin

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Clopidogrel

Results from studies in healthy subjects have shown a 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 by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

It is, however, uncertain to what extent this interaction is clinically important. One prospective, randomised (but incomplete) study (in over 3760 patients comparing placebo with omeprazole 20 mg in patients treated with clopidogrel and ASA) and non-randomised, post-hoc analyses of data from large, prospective, randomised clinical outcome studies (in over 47000 patients) did not show any evidence of an increased risk for adverse cardiovascular outcome when clopidogrel and PPIs, including omeprazole, were given concomitantly.

Results from a number of observational studies are inconsistent with regard to increased risk or no increased risk for CV thromboembolic events when clopidogrel is given together with a PPI.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA.

Other active substances

The absorption of 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 inhibits CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant medicines also metabolised by CYP2C19, such as diazepam, phenytoin, warfarin (R-warfarin) or other vitamin K antagonists and cilostazol, may be delayed.

Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. However, concomitant treatment with omeprazole capsules 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with this medicine.

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. Concomitant treatment with omeprazole 20 mg daily did, however, not change coagulation time in patients on continuous treatment with warfarin.

Cilostazol

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Other

Omeprazole is partly metabolised also by CYP3A4, but omeprazole does not inhibit this enzyme. Thus, omeprazole does not affect the metabolism of medicines metabolised by CYP3A4, such as cyclosporin, lidocaine, quinidine, estradiol, erythromycin, and budesonide. However, omeprazole has been shown to induce CYP1A2-mediated metabolism of clozapine. Close monitoring of plasma clozapine levels is recommended.

Results from a range of interaction studies with omeprazole versus other medicines demonstrate that omeprazole, 20-40 mg daily, has no significant influence on any other CYP enzymes relevant for medicine metabolism, as shown by the lack of metabolic interaction with substrates for CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as S-warfarin, piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol, propranolol), CYP2E1 (such as ethanol).

Unknown mechanism:

Tacrolimus

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus.

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.

Saquinavir

For other antiretroviral medicines, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral medicines of which unchanged serum levels have been reported when given with omeprazole.

Effects of other medicines on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP2C19 or CYP3A4 or both (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing the rate of omeprazole's metabolism.

Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. Since high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not required during temporary concomitant use.

Inducers of CYP2C19 and/or CYP3A4

Medicines known to induce CYP 2C19 or CYP 3A4 or both (such as rifampicin) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omezol IV can be used during pregnancy.

Breast-feeding

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

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Omezol IV is not likely to affect the ability to drive or use machines.

4.8 Undesirable effects

The following adverse reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency (common >1/100, <1/10; uncommon >1/1000, <1/100; rare >1/10000, <1/1000; very rare <1/10000; not known, cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

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

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very rare: Hypomagnesaemia, hypocalcaemia, hypokalaemia. severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, confusion, depression, 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, microscopic colitis

Not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritus, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Interstitial nephritis

Reproductive system and breast disorders

Rare: Gynaecomastia

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Omeprazole IV 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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proton pump inhibitor, ATC code: A02BC01

Mechanism of action

Omezol IV (omeprazole), a racemic mixture of two active 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 rapid 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 the stimulus.

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%.

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 *Helicobacter pylori*

See omeprazole capsules datasheet for information.

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* and possibly also *Clostridium difficile* in hospitalised patients.

5.2 Pharmacokinetic properties

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value is also seen in patients with renal insufficiency. In elderly patients, and in patients with hepatic insufficiency, the volume of distribution is slightly decreased. The plasma protein binding of omeprazole is about 95%.

Biotransformation

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed, specific isoform 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.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

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 oral once daily dosing. 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). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration.

No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an intravenously given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from bile secretion.

Special patient populations

Poor metabolisers

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 dosage of Omezol IV.

Renal impairment

The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Hepatic impairment

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.

Elderly

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

Paediatric

There is limited experience with omeprazole for intravenous use in children.

5.3 Preclinical safety data

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid

inhibition. Similar findings have been made after treatment with H_2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual drug.

6. Pharmaceutical Particulars

6.1 List of excipients

Each Omezol IV vial also contains

- disodium edetate 1.5 mg
- sodium hydroxide q.s. for pH adjustment.

6.2 Incompatibilities

None known when instructions in section 4.2 are followed.

6.3 Shelf life

Unopened product: 18 months.

Reconstituted product: Substance for infusion must be reconstituted with 5 mL of saline or 5 mL of 5% dextrose, then further diluted to 100 mL with saline for infusion or 5% dextrose for infusion.

Chemical and physical in-use stability has been demonstrated for 12 hours after reconstitution with saline or for 6 hours after reconstitution with 5% dextrose in a PVC bag.

From a microbiological point of view, the product should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. The solution can be handled at normal indoor light without special precaution.

6.4 Special precautions for storage

Unopened product: Store in original packaging at a temperature not exceeding 25°C, protected from light.

Reconstituted product: For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

Omezol IV is available in a pack of 5 glass vials of lyophilised powder.

6.6 Special precautions for disposal and other handling

For instructions on reconstitution of the product before administration, see section 4.2.

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

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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9. Date of First Approval

3 June 2010

10. Date of Revision of the Text

12 September 2023

Summary table of changes

Section	Summary of new information
4.4	Addition of Hypomagnesaemia information
4.8	Addition of hypocalcaemia, hypokalaemia as an adverse effect