New Zealand Datasheet

1 PRODUCT NAME
OMEPRAZOLE Injection 40 mg (Dr. Reddy's)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Omeprazole 40 mg for intravenous injection

3 PHARMACEUTICAL FORM
Omeprazole Injection 40 mg. Each vial contains a white to off-white lyophilised powder consisting of omeprazole sodium 42.6 mg, equivalent to omeprazole 40 mg, which is intended to be reconstituted with the diluent provided. No other injection solution should be used. The cap is aluminium with a white coloured plastic flip-off lid.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Omeprazole Injection 40 mg 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
In patients with duodenal ulcer, gastric ulcer or reflux oesophagitis where oral medication is inappropriate, Omeprazole Injection 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.

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

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

Elderly
Dose adjustment is not needed in the elderly.

Children
There is limited experience with omeprazole IV in children.

Method of Administration
Omeprazole Injection 40 mg should be given as a slow intravenous injection. The solution for IV injection is obtained by adding to the vial 10 mL of the solvent provided. (No other solvent should be used). Discoloration may occur if incorrect reconstitution technique is used. For practical information about the reconstitution see the package insert. 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. The solution should be used within 4 hours of reconstitution.

4.3 Contraindications
Known hypersensitivity to omeprazole.

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.

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 orally, 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, oestradiol, 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). However, omeprazole has been shown to induce CYP1A2-mediated metabolism of clozapine. Close monitoring of plasma clozapine levels is recommended.

Unknown mechanism:
Tacrolimus
Concomitant administration of omeprazole and tacrolimus may 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 CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP 2C19 or CYP 3A4 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. Omeprazole 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.

4.7 Effects on ability to drive and use machines
Omeprazole is not likely to affect the ability to drive or use machines.

4.8 Undesirable effects
Omeprazole is well tolerated and adverse reactions have generally been mild and reversible. The following events 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.

The following definitions of frequencies are used:

Common ≥1/100

Uncommon ≥1/1,000 and <1/100

Rare <1/1,000

Common	Central and peripheral nervous system:	Headache
	Gastrointestinal:	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
Uncommon	Central and peripheral nervous system:	Dizziness, paraesthesia, somnolence
	Hepatobiliary disorders:	Increased liver enzymes
	Skin:	Rash, dermatitis pruritis, urticaria
	Other:	Malaise
Rare	Central and peripheral nervous system:	Taste disturbance
	Endocrine:	Gynaecomastia
	Gastrointestinal:	Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis
	Haematological:	Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
	Hepatobiliary disorders:	Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure
	Musculoskeletal:	Arthralgia, muscular weakness and myalgia
	Skin:	Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia, DRESS (drug rash with eosinophilia and systemic symptoms)
	Immune system disorders:	Hypersensitivity reactions e.g. angioedema, fever, and anaphylactic reaction/shock.
	Ear and labyrinth disorders:	Vertigo
	Metabolism and nutrition disorders:	Hyponatraemia
	Psychiatric disorders:	Agitation, aggression, confusion, depression, hallucinations
	Eye disorders:	Blurred vision
	Respiratory, thoracic and mediastinal disorders:	Bronchospasm
	Renal and urinary disorders:	Interstitial nephritis
	Reproductive system and breast disorders:	Gynaecomastia
	General disorders and administration site conditions:	Increased sweating, peripheral oedema.
Very Rare	Metabolism and	Hypomagnesaemia, severe hypomagnesaemia

	nutrition disorders:	may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.
Frequency not known	Gastrointestinal:	Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

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 casual 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC01

Omeprazole is 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.

Site and mechanism of action
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.

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*.

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%.

Metabolism and excretion
The average half-life of the terminal phase of the plasma concentration-time curve following IV administration of omeprazole is approximately 40 minutes. The total plasma clearance is 0.3 to 0.6 L/min. There is no change in half-life during treatment.

Omeprazole is completely metabolised by the cytochrome P450 system (CYP), mainly in the liver. The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19 (S-mephenytoin hydroxylase), responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. In accordance with this, as a consequence of competitive inhibition, there is a potential for metabolic drug-drug interactions between omeprazole and other substrates for CYP2C19.

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.

The elimination of omeprazole is unchanged in patients with reduced renal function.

The elimination half-life is increased in patients with impaired liver function, but omeprazole has not shown any accumulation with once daily dosing.

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 vial contains disodium edetate 1.0 mg and sodium hydroxide q.s. for pH adjustment.

The 10 ml diluent contains Macrogol 400, citric acid monohydrate and water for injections.

6.2 Incompatibilities
None known when instructions in section 4.2 are followed.

6.3 Shelf life
Unopened packages: 2 years at a temperature not exceeding 25ºC.

6.4 Special precautions for storage
Omeprazole for Injection must be dissolved in the 10 ml of diluent provided.

Chemical and physical in-use stability has been demonstrated for 4 hours after reconstitution.

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. Any unused portion should be discarded.

6.5 Nature and contents of container
Omeprazole Injection 40 mg for Injection: 5 vials of lyophilised powder and 5 10 ml diluent ampoules.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
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9 DATE OF FIRST APPROVAL
15 January 2009

10 DATE OF REVISION OF THE TEXT
7 December 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Inclusion of DRESS (drug rash with eosinophilia and systemic symptoms) as a rare event