

## New Zealand Datasheet

### Name of Medicine

OMEPRAZOLE Injection 40 mg (Dr. Reddy's)

Omeprazole 40 mg for intravenous injection

### Presentation

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.

### Uses

#### Actions

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<sup>+</sup>,K<sup>+</sup>-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*.

## **Pharmacokinetics**

### **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.

## **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.

## **Dosage and 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.

### **Contraindications**

Known hypersensitivity to omeprazole.

### **Warnings and Precautions**

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.

### **Use in Pregnancy and Lactation**

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.

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 machines**

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

### **Adverse 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

<b>Common</b>	Central and peripheral nervous system:	Headache
	Gastrointestinal:	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
<b>Uncommon</b>	Central and peripheral nervous system:	Dizziness, paraesthesia, somnolence, insomnia and vertigo
	Hepatic:	Increased liver enzymes
	Skin:	Rash, dermatitis and/or pruritis. Urticaria

<b>Rare</b>	Other:	Malaise
	Central and peripheral nervous system:	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients
	Endocrine:	Gynaecomastia
	Gastrointestinal:	Dry mouth, stomatitis and gastrointestinal candidiasis
	Haematological:	Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
	Hepatic:	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
	Other:	Hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

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.

## Interactions

The absorption of some medicines might be altered due to the decreased intragastric acidity. Thus it can be predicted that the absorption of ketoconazole and itraconazole can decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

As omeprazole is metabolised in the liver through cytochrome P450 2C19 (CYP2C19), it can prolong the elimination of diazepam, phenytoin, warfarin (R-warfarin) and other vitamin K antagonists, which are all in part substrates for this enzyme.

Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. However concomitant treatment with omeprazole 20 mg orally, 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.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration but there is no interaction with metronidazole or

amoxicillin. These antimicrobials are used together with omeprazole for eradication of *Helicobacter pylori*.

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir.

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. However, a dose adjustment of omeprazole was not required.

Results from a range of interaction studies with omeprazole versus other medicines indicate that omeprazole orally, 20-40 mg daily, has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lidocaine, quinidine, estradiol, erythromycin, budesonide)

## **Overdosage**

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.

## **Pharmaceutical Precautions**

Shelf life: Unopened packages: 2 years at a temperature not exceeding 25°C.

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.

## **Incompatibilities**

None known when instructions in Dosage and Administration are followed.

## **Medicine Classification**

Prescription Medicine.

## **Package Quantities**

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

## **Further Information**

### **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.

### **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<sub>2</sub>-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual drug.

### **Name and Address**

Dr Reddy's New Zealand Ltd  
Level 6, AMI House  
63 Albert Street  
PO Box 911-267  
AUCKLAND

Tel: (09) 356 7000  
Fax: (09) 356 7001

### **Date of Preparation**

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