

# New Zealand Datasheet

## 1 PRODUCT NAME

Dr Reddy's Omeprazole

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Omeprazole 20 mg capsules

## 3 PHARMACEUTICAL FORM

Omeprazole capsules 20 mg: hard gelatine size 2 capsules with a light grey opaque body printed with "R158" in black ink, and a purple opaque cap printed with "Omeprazole 20 mg" in black ink. Each capsule contains omeprazole 20 mg as enteric coated pellets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Dr Reddy's Omeprazole capsules are for the short-term relief of gastric reflux-like symptoms in sufferers aged 18 years and over.

### 4.2 Dose and method of administration

Dr Reddy's Omeprazole capsules are recommended to be given in the morning and swallowed whole with half a glass of water. The contents of the capsule should not be chewed or crushed.

For patients with swallowing difficulties the capsule can be opened and the contents swallowed directly with half a glass of liquid or after mixing the contents in a slightly acidic fluid e.g. fruit juice, yoghurt or in non carbonated water. The dispersion should be taken immediately or within 30 minutes. Alternatively patients can suck the capsule and swallow the pellets with liquid. The pellets must not be chewed or crushed.

### Reflux oesophagitis

The recommended dosage is one Dr Reddy's Omeprazole capsule 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. The maximum daily dose should not exceed 20 milligrams.

### Impaired Renal Function

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

### Impaired Hepatic Function

As bioavailability and plasma half-life of omeprazole are 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.

### 4.3 Contraindications

Known hypersensitivity to omeprazole.

### 4.4 Special warnings and precautions for use

Dr Reddy's Omeprazole 20 mg capsules are for short-term use only, except on medical advice. Do not use the medicine for any purpose other than that specified on the pack, except on medical advice.

Do not use in those that are experiencing weight loss, persistent regurgitation of food or vomiting, difficulty swallowing or symptoms of gastro-intestinal bleeding, except on medical advice.

Consult a doctor if symptoms persist, recur or worsen or if new symptoms occur. Consult a doctor or pharmacist before use if you are pregnant or are taking any other medicines.

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 medicines may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

#### 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 healthcare professional should consider stopping pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

### 4.5 Interaction with other medicines and other forms of interaction

No interaction with food or concomitantly administered antacids has been found.

#### **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 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 capsules 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, lignocaine, 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 and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

## **4.6 Fertility, 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. Dr Reddy's Omeprazole capsules can be used during pregnancy.

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**

Dr Reddy's Omeprazole capsules are not likely to affect the ability to drive or use machines.

## **4.8 Undesirable effects**

Dr Reddy's Omeprazole capsules are 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: Gastrointestinal:	Headache Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence
<b>Uncommon</b>	Central and peripheral nervous system:  Hepatobiliary disorders: Skin:  Psychiatric disorders: Other:	Dizziness, paraesthesia, somnolence  Increased liver enzymes Rash, dermatitis, pruritis, urticaria Insomnia Malaise
<b>Rare</b>	Central and peripheral nervous system: Endocrine: Gastrointestinal:  Haematological:  Hepatobiliary disorders:  Musculoskeletal: Skin:  Immune system disorders:  Ear and labyrinth disorders:  Metabolism and nutrition disorders:	Taste disturbance Gynaecomastia Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia. Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure Arthralgia, muscular weakness and myalgia Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock Vertigo 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,
<b>Very Rare</b>	Metabolism and nutrition disorders:	Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.
<b>Frequency not known</b>	Skin and subcutaneous tissue disorders	Subacute cutaneous lupus erythematosus.

#### 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

Rare reports have been received of overdosage with omeprazole. 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 from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection to omeprazole overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment has been needed.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand, call 0800 764 766.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC-code: A02BC01

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.

#### **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**

Oral dosing with omeprazole capsules once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole capsules 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% twenty-four hours after dosing.

Oral dosing with omeprazole capsules 20 mg maintains an intragastric pH of  $\geq 3$  for a mean time of 17 hours of the 24 hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalises acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease.

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**

### **Absorption and distribution**

Omeprazole is acid labile and is therefore administered orally as enteric-coated pellets in capsules or tablets.

Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of omeprazole capsules is approximately 35%. After repeated once daily administration, the bioavailability increases to about 60%. 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. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

### **Metabolism and excretion**

After oral administration, the plasma elimination half-life of omeprazole is usually shorter than one hour and there is no change in half-life during long-term 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 orally given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from bile secretion.

The systemic bioavailability and elimination of omeprazole is unchanged in patients with reduced renal function. The area under the plasma concentration-time curve, and the elimination half-life are increased in patients with impaired liver function, but omeprazole has not shown any tendency to accumulate 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<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.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol, Crospovidone, Hypromellose, Poloxamer, Meglumine, Povidone, Methacrylic acid ethyl acrylate copolymer, Triethyl citrate, Magnesium stearate,  
The gelatin capsules consist of Erythrosin, Patent blue V, Titanium dioxide, Gelatin, and printing ink.

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

Shelf life is 36 months (3 years) from manufacture.

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

20 mg: Cartons of aluminium blisters containing 14 or 28 capsules.

### **6.6 Special precautions for disposal**



## **7 MEDICINE SCHEDULE**

Pharmacy Only Medicine.

## **8 SPONSOR**

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## **9 DATE OF FIRST APPROVAL**

20 May 2010

## **10 DATE OF REVISION OF THE TEXT**

5 May 2017

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information