SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

OMEZ 10, 10 mg, capsule

OMEZ 20, 20 mg, capsule

OMEZ 40, 40 mg, capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OMEZ 10: Each capsule contains omeprazole 10 mg

OMEZ 20: Each capsule contains omeprazole 20 mg

OMEZ 40: Each capsule contains omeprazole 40 mg

Contains sugar (mannitol).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

OMEZ 10: Off-white to pale yellow elliptical to spherical enteric-coated pellets, filled in a hard gelatin capsule with opaque lavender coloured cap and opaque yellow coloured body. "Omeprazole 10 mg" imprinted with black ink on cap and "R157" imprinted with black ink on body.

OMEZ 20: Off-white to pale yellow elliptical to spherical enteric-coated pellets, filled in a hard gelatin capsule with opaque lavender coloured cap and opaque iron grey coloured body. "Omeprazole 20 mg" imprinted with black ink on cap and "R158" imprinted with black ink on body.

OMEZ 40: Off-white to pale yellow elliptical to spherical enteric-coated pellets, filled in a hard gelatin

capsule with opaque yellow coloured cap and opaque purple coloured body. "Omeprazole 40 mg" imprinted with black ink on cap and "R159" imprinted with black ink on body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OMEZ is indicated in:

Adults

- Treatment of duodenal ulcer, including prevention of relapse, gastric ulcer and reflux oesophagitis.
- Long-term management of reflux oesophagitis and Zollinger-Ellison Syndrome.
- Symptomatic relief of heartburn in patients with gastro-oesophageal reflux disease (GORD) and the short-term relief of functional dyspepsia.
- *Helicobacter pylori*-positive duodenal ulcers as part of an eradication programme with appropriate antibiotics.
- Treatment of non-steroidal anti-inflammatory drugs (NSAID)-associated gastric and/or duodenal ulcer/erosions.
- Reduction of the risk to develop gastric and/or duodenal ulcer/erosions and reduction of the risk of relapse for previously healed gastric and/or duodenal ulcer/erosions in patients on NSAID treatment.

Children

Short-term (up to 3 months) treatment of severe ulcerative reflux oesophagitis resistant to previous medical treatment.

4.2 Posology and method of administration

Posology

RECOMMENDED DOSAGES FOR ADULTS

Duodenal ulcer

20 mg once daily for two to four weeks.

In some duodenal ulcer patients refractory to other treatment regimens,

40 mg once daily may be effective.

Prevention of relapse in patients with duodenal ulcer

10 mg once daily.

If necessary the dose can be increased to 20 to 40 mg once daily.

The above recommended dosage regimens are inclusive of *Helicobacter pylori*-positive duodenal ulcers as part of the eradication programme with appropriate antibiotics.

Gastric ulcer and reflux oesophagitis

20 mg once daily for four to eight weeks.

In some gastric ulcer and reflux oesophagitis patients refractory to other treatment regimens, 40 mg once daily may be effective.

For the long-term management of patients with reflux oesophagitis the recommended dose is 20 mg once daily. If necessary the dose can be increased to 20 to 40 mg once daily.

In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with OMEZ at a dosage of 20 mg once daily.

NSAID-associated gastro-duodenal lesions with or without continued NSAID treatment

20 mg once daily.

In most patients healing occurs within 4 weeks. For patients who may not be fully healed after the initial course healing usually occurs during a further 4 weeks of treatment.

Prevention of NSAID-associated gastro-duodenal lesions and dyspeptic symptoms

20 mg once daily.

Symptomatic gastro-oesophageal reflux disease

20 mg daily.

Patients may respond adequately to 10 mg daily; therefore individual dose adjustments should be

considered.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose further investigation is recommended.

Zollinger-Ellison Syndrome

60 mg once daily.

The dosage should be adjusted individually and treatment continued as long as it is clinically indicated.

With doses above 80 mg daily the dose should be divided and given twice daily.

There is very limited experience with the use of OMEZ in children (see Section 4.4).

Severe ulcerative reflux oesophagitis in children from one year and older

Recommended dosages:

Weight:	Dosage:
10 to 20 kg:	10 mg once daily. If needed increase to 20 mg once daily.
> 20 kg:	20 mg once daily. If needed increase to 40 mg once daily.

Special populations

Elderly

Dose reductions are not necessary in elderly patients.

The long-term safety of OMEZ in patients with renal and hepatic impairment has not been established (see Section 4.4).

Impaired renal function

Dose reductions are not necessary in renal impairment.

Impaired hepatic function

Bioavailability and plasma half-life of OMEZ are increased in patients with impaired hepatic function, therefore a daily dose of 10 to 20 mg is generally sufficient.

Method of administration

OMEZ is recommended to be given in the morning and swallowed whole with a half glass of liquid. The capsules should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to omeprazole or to any of the other ingredients of OMEZ.

Safety in pregnancy and lactation has not been established.

OMEZ must not be used concomitantly with nelfinavir.

Co-administration of atazanavir with OMEZ is not recommended.

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, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Hepatic impairment may require a reduction in dose (see Section 4.2).

The long-term safety of OMEZ in patients with renal and/or hepatic impairment has not been established.

There is very limited experience with the use of OMEZ in children.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see Section 4.3). If the combination of atazanavir with OMEZ is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir;

omeprazole 20 mg should not be exceeded.

OMEZ, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

OMEZ is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and OMEZ (see Section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of OMEZ and clopidogrel should be discouraged.

Increased risk of bone fractures:

OMEZ, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 to 40 %. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Increased risk of hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like OMEZ for at least three months, and in most cases for a year.

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 OMEZ.

For patients expected to be on prolonged treatment or who take OMEZ with digoxin or drugs that may

cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting OMEZ treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitor (PPI) therapy like OMEZ is 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 health care professional should consider stopping OMEZ. SCLE after previous treatment with OMEZ may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, OMEZ treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of OMEZ treatment.

Effects related to acid inhibition

During long-term treatment gastric glandular cysts have been reported in increased frequency. These physiological changes result from pronounced inhibition of gastric acid secretion. Decreased gastric acidity increases gastric counts of bacteria normally present in the gastro-intestinal tract.

Treatment with OMEZ may lead to an increased risk of gastro-intestinal infections such as *Salmonella*, *Campylobacter*, or *C. difficile*.

Clostridium-difficile-associated diarrhoea

Proton pump inhibitor (PPI) therapy like OMEZ may be associated with an increased risk of Clostridium difficile associated diarrhoea (CDAD), especially in hospitalised patients.

This diagnosis should be considered for diarrhoea that does not improve (see Section 4.8).

Patients should use the lowest dose and shortest duration of OMEZ therapy appropriate to the condition

being treated.

Acute Tubulointerstitial Nephritis

Acute Tubulointerstitial Nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. TIN is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury. TIN may be drug-related, infectious, systemic, autoimmune, genetic, and idiopathic with the most common cause being related to a medication or drug exposure.
Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decrease renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extrarenal manifestations (e.g., fever rash or arthralgia). Discontinue OMEZ and evaluate patients with suspected acute TIN.

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

OMEZ contains mannitol which, on rare occasions, may cause hypersensitivity reactions and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Clopidogrel:

Clopidogrel is metabolised to its active metabolite in part by CYP2C19. Co-administration of clopidogrel with omeprazole, an inhibitor of CYP2C19, reduces the pharmacological activity of clopidogrel given concomitantly or 12 hours apart. Concomitant use of medicines that inhibit the activity of this enzyme may result in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

OMEZ is metabolised via the hepatic P450 cytochrome enzyme system, which may affect the metabolism of other medications metabolised by these enzymes, when given concomitantly.

The elimination of diazepam, warfarin and phenytoin may be prolonged when OMEZ is given concomitantly. Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when OMEZ is given concomitantly.

There may be interactions with other medicines, which are also metabolised via the cytochrome P450 enzyme system.

Digoxin:

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 %. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced (see Section 4.4).

Nelfinavir and atazanavir:

In case of co-administration with OMEZ, the plasma levels of nelfinavir and atazanavir are decreased. Concomitant administration of OMEZ with nelfinavir is contraindicated (see Section 4.3).

Co-administration of OMEZ (40 mg once daily) reduced mean nelfinavir exposure by ca. 40 % and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 to 90 %. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended. Concomitant administration of OMEZ (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75 % decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of OMEZ (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30 % in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Tacrolimus:

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

A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should

be performed, and dosage of tacrolimus adjusted if needed.

Methotrexate:

When given together with OMEZ, 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.

Other active substances:

The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see Section 4.3).

4.7 Effects on ability to drive and use machines

OMEZ may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

Infections and Infestations

Frequency not known: Clostridium-difficile-associated diarrhea

Blood and lymphatic system disorders

Less frequent: Leucopenia, thrombocytopenia, agranulocytosis, pancytopenia

Endocrine disorders

Less frequent: Gynaecomastia

Metabolic and nutritional disorders

Less frequent: Hyponatraemia, hypomagnesaemia.

Psychiatric disorders

Less frequent: Reversible mental confusion, agitation, aggression, depression and hallucinations (predominantly in severely ill patients)

Nervous system disorders

Frequent: Headache (severe enough to cause discontinuation in some patients)

Less frequent: Dizziness, somnolence, insomnia, parasthaesias

Eye disorders

Less frequent: Blurred vision

Vascular disorders

Less frequent: Peripheral oedema

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm

Gastrointestinal disorders

Frequent: Diarrhoea (severe enough to require discontinuation of therapy in some patients), constipation, abdominal pain or colic, nausea, vomiting, flatulence, gastric glandular cysts, fundic gland polyps (benign)

Less frequent: Dry mouth, stomatitis, oesophageal candidiasis, taste disturbances

Frequency unknown: microscopic colitis

Hepato-biliary disorders

Less frequent: Raised liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, urticaria, pruritus, photosensitivity, bullous eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, alopecia, erythema multiforme

Musculoskeletal, connective tissue and bone disorders

Less frequent: Asthenia, arthralgia, myalgia, bone fracture

Renal and urinary disorders

Less frequent: Interstitial nephritis

Immune system disorders

Less frequent: Hypersensitivity reactions (e.g. fever, angioedema, bronchospasm, interstitial nephritis)

General disorders and administration site conditions

Less frequent: Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Blurred vision, confusion, diaphoresis, flushing, headache, malaise, nausea and tachycardia have been reported from over-dosage with omeprazole. There is no specific antidote for overdose with omeprazole. TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

Due to extensive protein binding omeprazole is not readily dialysable. Patients in whom overdose is confirmed or suspected should be referred for medical practitioner/doctor consultation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

11.4.3 Medicines acting on the gastrointestinal tract – Other

Omeprazole is an inhibitor of the gastric proton pump (H+, K+-ATPase). It inhibits both basal and stimulated gastric acid secretion by parietal cells, whether induced by acetylcholine, gastrin or histamine. Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

5.2 Pharmacokinetic properties

Orally administered omeprazole is well absorbed but to a variable extent. Absorption of omeprazole takes place in the small intestine and is usually completed within three to six hours. Bioavailability depends on dose and gastric pH and may reach 70 % with repeated administration. Food has no influence on the bioavailability of omeprazole.

Omeprazole is more than 95 % bound to plasma proteins. Clearance from the circulation is by hepatic metabolism with a plasma half-life of 30 to 90 minutes. Hepatic metabolism occurs primarily via the cytochrome P450 (CYP) isoform (CYP2C19). The inactive metabolites are excreted mainly in the urine (80 %) whilst the remaining 20 % are excreted via the faeces. The average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in plasma half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) and not to the actual plasma concentration at a given time.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Hydroxypropyl methyl cellulose

Magnesium stearate

Mannitol

Meglumine

Methacrylic acid co-polymer (Type C)

Poloxamer

Povidone

Triethyl citrate.

<u>Capsule shells:</u>

D&C red #28

FD&C blue #1

FD&C red #40

FD&C yellow #6

Gelatin

Titanium dioxide.

In addition the 10 mg and 40 mg capsule shells also contain Yellow iron oxide and the 20 mg capsule shells contain black iron oxide.

The black printing ink:

Black iron oxide

D&C Yellow No. 10 aluminium lake

FD&C Blue No. 1 aluminium lake

FD&C Blue No. 2 aluminium lake

FD&C Red No. 40 aluminium lake

Pharmaceutical glaze

Propylene glycol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the blisters in the outer carton until required for use.

The containers must be tightly closed.

6.5 Nature and contents of container

OMEZ 10: Blister packaging containing 30 or 100 capsules.

White HDPE bottles containing 30 or 100 capsules.

OMEZ 20: Blister packaging containing 14, 30 or 100 capsules.

White HDPE bottles containing 14, 30, 100 or 1000 capsules.

OMEZ 40: Blister packaging containing 14, 28, 30 or 100 capsules.

White HDPE bottles containing 30, 100 or 500 capsules.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

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2057

8 REGISTRATION NUMBERS

OMEZ 10: 34/11.4.3/0299

OMEZ 20: 34/11.4.3/0300

OMEZ 40: 34/11.4.3/0301

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 June 2001

10 DATE OF REVISION OF TEXT

05 September 2023