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 10 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 four weeks. For patients who may not be fully healed after the initial course, healing usually occurs during a further four 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 (see Section 6.1).

Safety in pregnancy and lactation has not been established.

OMEZ must not be used concomitantly with nelfinavir or atazanavir (see Section 4.5).

OMEZ should not be administered with St. John's Wort (see Section 4.5).

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 melaena) 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 4.5).

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 avoided.

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 *Clostridium 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.

Excipients:

Mannitol:

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

Effects of omeprazole on the pharmacokinetics of other active substances

Active substances with pH dependent absorption:

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Clopidogrel:

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose / 75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, at the same time as clopidogrel).

The exposure to the active metabolite of clopidogrel was decreased by 46 % (Day 1) and 42 % (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47 % (24 hours) and 30 % (Day 5) when clopidogrel and omeprazole were administered together. The consequence of this would be a reduction in the antiplatelet activity of clopidogrel, which may predispose to an increase in cardiovascular events. As a precaution, concomitant use of omeprazole and clopidogrel should be avoided (see Section 4.4).

Digoxin:

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 %. Digoxin toxicity has been reported. 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.

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.

Active substances metabolised by CYP2C19:

OMEZ is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such medicines are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin. Monitoring of INR is recommended and dosage reductions may be necessary when OMEZ is given concomitantly.

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.

Phenytoin:

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating OMEZ treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending OMEZ treatment.

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

Unknown mechanism:

Saquinavir

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70 % for saquinavir. Caution is advised with concomitant use of saquinavir/ritonavir.

Tacrolimus:

Concomitant administration of omeprazole 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 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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4:

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated, adjustment of the OMEZ dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term

treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4:

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St.John's Wort may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism and should not be used concomitantly with OMEZ.

4.6 Fertility, pregnancy and lactation

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

Omeprazole is excreted in breast milk.

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

Summary of the safety profile

The most frequent undesirable effects are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

Infections and Infestations

Frequency not known: Clostridium-difficile-associated diarrhoea.

Blood and lymphatic system disorders

Less frequent: Leucopaenia, thrombocytopaenia, agranulocytosis, pancytopaenia.

Immune system disorders

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

Metabolic and nutritional disorders

Less frequent: Hyponatraemia.

Frequency unknown: Hypomagnesaemia. Severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

Psychiatric disorders

Less frequent: Confusion, agitation, aggression, insomnia and hallucinations have occurred (predominantly in severely ill patients).

Nervous system disorders

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

Less frequent: Dizziness, somnolence, parasthaesias, taste disturbances.

Eye disorders

Less frequent: Blurred vision.

Ear and labyrinth disorders

Less frequent: Vertigo.

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, gastrointestinal candidiasis, acid regurgitation and increased gastro-intestinal bacteria.

Frequency unknown: microscopic colitis.

Hepato-biliary disorders

Less frequent: Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease.

Skin and subcutaneous tissue disorders

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

Frequency unknown: Subacute cutaneous lupus erythematosus (see Section 4.4).

Musculoskeletal, connective tissue and bone disorders

Less frequent: Asthenia, arthralgia, myalgia, muscle weakness, fracture of the hip, wrist or spine.

Renal and urinary disorders

Less frequent: Interstitial nephritis (may progress to acute kidney injury and/or chronic renal failure and symptoms of interstitial nephritis may persist even when treatment with PPI is terminated).

Reproductive system and breast disorders

Less frequent: Gynaecomastia.

General disorders and administration site conditions

Less frequent: Increased sweating, peripheral oedema, 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

There is limited information available on the effects of overdoses of omeprazole in humans. 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 2400 mg omeprazole (120 times the usual recommended clinical dose).

Blurred vision, diaphoresis, flushing, headache, malaise, nausea, vomiting, dizziness, abdominal pain, diarrhoea and tachycardia have been reported. Also apathy, depression and confusion have been described in single cases.

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

Pharmacotherapeutic group:

Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

Mechanism of action

Omeprazole, a racemic mixture of two 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 rapidly 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 stimulus.

Omeprazole has no effect on acetylcholine, histamine or gastrin receptors.

Pharmacodynamic effects

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion

Oral dosing with omeprazole 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 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 % 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 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 gastroesophageal 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.

Effect on H. pylori

H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease.

H. pylori is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.

Eradication of *H. pylori* with omeprazole and antimicrobials is associated with high rates of healing and long-term remission of peptic ulcers.

Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.

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 medicinal products may lead to slightly increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* possibly also *Clostridium difficile*.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

Paediatric population

In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0,7 to 1,4 mg/kg improved oesophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0 to 24 months with clinically diagnosed gastroesophageal reflux disease were treated with 0,5, 1,0 or 1,5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50 % after 8 weeks of treatment irrespective of the dose.

Eradication of H. pylori in children

A randomised, double blind clinical study (Héliot study) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis: *H. pylori* eradication rate: 74,2 % (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9,4 % (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

5.2 Pharmacokinetic properties

Absorption

Orally administered omeprazole is well absorbed but to a variable extent.

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets.

Absorption of omeprazole rapid, with peak plasma levels occurring approximately 1 to 2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3 to 6 hours. Concomitant intake of food has no influence on the bioavailability of omeprazole. The systemic availability (bioavailability), from a single oral dose of omeprazole (depends on dose and gastric pH) is approximately 40 %. After repeated once-daily administration, the bioavailability increases to about 60 %.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0,3 l/kg body weight.

Omeprazole is more than 97 % plasma protein bound.

Biotransformation

Clearance from the circulation is by hepatic metabolism with a plasma half-life of 30 to 90 minutes. Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed 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 medicine-medicine 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. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3 % of the Caucasian population and 15 to 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 posology of omeprazole.

Elimination

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.

Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80 % of an oral dose of omeprazole is excreted as metabolites in the urine the remaining 20 % in the faeces, primarily originating from bile secretion.

Linearity/non-linearity

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. 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).

No metabolite has been found to have any effect on gastric acid secretion.

Special populations

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.

Renal impairment

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

Elderly people

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

Paediatric population

During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

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.

Capsule shells:

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

Morningside

Sandton

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

23 April 2024