SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

OMEZ OTC 20, 20 mg, capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OMEZ OTC 20: Each capsule contains omeprazole 20 mg

Contains sugar (mannitol).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

OMEZ OTC 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OMEZ OTC 20 is indicated for the temporary, short-term relief of heartburn and hyperacidity in adults.

4.2 Posology and method of administration

Posology

RECOMMENDED DOSAGES FOR ADULTS

20 mg once daily.

OMEZ OTC 20 has a maximum daily dose of 20 mg.

Do not use continuously for more than 14 days without consulting a doctor.

Special populations

Elderly

Dose reductions are not necessary in elderly patients.

The long-term safety of OMEZ OTC 20 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 OTC 20 is increased in patients with impaired hepatic function, therefore a daily dose of 10 to 20 mg is generally sufficient.

Method of administration

OMEZ OTC 20 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 OTC 20 (see Section 6.1).

Safety in pregnancy and lactation has not been established.

OMEZ OTC 20 must not be used concomitantly with nelfinavir or atazanavir (see Section 4.5).

OMEZ OTC 20 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 OTC 20 in patients with renal and/or hepatic impairment has not been established.

There is very limited experience with the use ofOMEZ OTC 20 in children.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see Section 4.5)

OMEZ OTC 20, 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 OTC 20 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 OTC 20 (see Section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of OMEZ OTC 20 and clopidogrel should be avoided.

<u>Increased risk of bone fractures:</u>

OMEZ OTC 20, 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 OTC 20 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 OTC 20.

For patients expected to be on prolonged treatment or who take OMEZ OTC 20 with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting OMEZ OTC 20 treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitor (PPI) therapy like OMEZ OTC 20 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 OTC 20. SCLE after previous treatment with OMEZ OTC 20 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 OTC 20 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 OTC 20 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 OTC 20 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 OTC 20 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 OTC 20 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 OTC 20 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 OTC 20 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 OTC 20, the plasma levels of nelfinavir and atazanavir are decreased.

Concomitant administration of OMEZ OTC 20 with nelfinavir is contraindicated (see Section 4.3). Co-administration of omeprazole (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 omeprazole (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 omeprazole (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 OTC 20 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 OTC 20 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 OTC 20 treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending OMEZ OTC 20 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 OMEZ OTC 20 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 OTC 20, 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 OTC 20 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 OTC 20.

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 OTC 20 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.

Blood and lymphatic system disorders

Less frequent: Leucopenia, thrombocytopenia, agranulocytosis, pancytopenia

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)

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

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

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 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

Capsule content:

Crospovidone

Hydroxypropyl methyl cellulose

Magnesium stearate

Mannitol

Meglumine

Methacrylic acid co-polymer (Type C)

Poloxamer

Povidone

Triethyl citrate.

Capsule shells:

Black iron oxide

D&C red #28

FD&C blue #1

FD&C red #40

FD&C yellow #6

Gelatin

Titanium dioxide.

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

Blister packaging containing 14 capsules.

White HDPE bottles containing 14 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.

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Morningside

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2057

8 REGISTRATION NUMBER

34/11.4.3/0297

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 June 2001

10 DATE OF REVISION OF TEXT

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