SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

OMEPRAZOLE DRL 20, 20 mg, capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OMEPRAZOLE DRL 20: Each capsule contains omeprazole 20 mg

Contains sugar (mannitol).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

OMEPRAZOLE DRL 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

OMEPRAZOLE DRL 20 is indicated for the treatment 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.

OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 20 is increased in patients with impaired hepatic function, therefore a daily dose of 10 to 20 mg is generally sufficient.

Method of administration

OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 20.

Safety in pregnancy and lactation has not been established.

OMEPRAZOLE DRL 20 must not be used concomitantly with nelfinavir.

Co-administration of atazanavir with OMEPRAZOLE DRL 20 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 OMEPRAZOLE DRL 20 in patients with renal and/or hepatic impairment has not been established.

There is very limited experience with the use of OMEPRAZOLE DRL 20 in children.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see Section 4.3). If the combination of atazanavir with OMEPRAZOLE DRL 20 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.

OMEPRAZOLE DRL 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.

OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 20 (see Section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of OMEPRAZOLE DRL 20 and clopidogrel

should be discouraged.

Increased risk of bone fractures:

OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 20.

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

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitor (PPI) therapy like OMEPRAZOLE DRL 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

OMEPRAZOLE DRL 20. SCLE after previous treatment with OMEPRAZOLE DRL 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, OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 20 may be associated with an increased risk of *Clostridium difficile* associated diarrhoea (CDAD), especially in metabolised 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 OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 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.

OMEPRAZOLE DRL 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

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.

OMEPRAZOLE DRL 20 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 OMEPRAZOLE DRL 20 is given concomitantly.

Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when OMEPRAZOLE DRL 20 is given concomitantly.

There may be interactions with other medicines, which are also metabolized 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 OMEPRAZOLE DRL 20, the plasma levels of nelfinavir and atazanavir are decreased.

Concomitant administration of OMEPRAZOLE DRL 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.

Tacrolimus:

Concomitant administration of OMEPRAZOLE DRL 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 OMEPRAZOLE DRL 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.

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

OMEPRAZOLE DRL 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

Infections and Infestations

Frequency not known: Clostridium-difficile-associated diarrhoea

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.

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.

Block B, 204 Rivonia Road

Morningside

Sandton

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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