SCHEDULING STATUS: S2

PROPRIETARY NAME AND DOSAGE FORM:

OMIFLUX 20 (capsules)

COMPOSITION:

Each Omiflux 20 capsule contains 20 mg omeprazole in a gastro-resistant formulation.

Excipients: gelatine, hypromellose, magnesium oxide heavy, methacrylic acid – ethyl achrylate copolymer 1:1 dispersion, povidone K25, sodium lauryl sulphate, talc and triethyl citrate.

Contains sugar (sucrose 43,350 mg).

PHARMACOLOGICAL CLASSIFICATION:

A 11.4.3 Medicines acting on gastrointestinal tract – Other

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

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 3 to 6 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.

INDICATIONS:

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

CONTRAINDICATIONS:

Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the ingredients of OMIFLUX 20.
Safety in pregnancy and lactation has not been established.
OMIFLUX 20 must not be used concomitantly with atazanavir or nelfinavir (see “INTERACTIONS”).

WARNINGS AND SPECIAL PRECAUTIONS:

Symptomatic response (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) to OMIFLUX 20 therapy does not preclude the presence of gastric ulcer or malignancy or a malignant disease of the oesophagus. The administration of OMIFLUX 20 in this situation may delay diagnosis.
Hepatic impairment may require a reduction in dose (see “DOSAGE AND DIRECTIONS FOR USE”).

There is very limited experience with the use of OMIFLUX 20 in children.
The long-term safety of OMIFLUX 20 in patients with renal and/or hepatic impairment has not been established.

OMIFLUX 20 may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressant agents.
An interaction is observed between clopidogrel and OMIFLUX 20. Concomitant use of OMIFLUX 20 and clopidogrel should be avoided.

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 OMIFLUX 20 may lead to an increased risk of gastro-intestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*. For patients using OMIFLUX 20, a diagnosis of *Clostridium difficile* associated diarrhoea (CDAD) should be considered with diarrhoea that does not improve. Patients should be advised to seek immediate care from a healthcare professional if they experience watery stools, abdominal pain and fever while taking OMIFLUX 20. Patients should use the lowest dose and shortest duration of OMIFLUX 20 therapy appropriate to the condition being treated.
In the presence of symptoms such as significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, or melaena, and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with OMIFLUX 20 may alleviate symptoms and delay diagnosis.

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Sucrose:

OMIFLUX 20 contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltse insufficiency should not take OMIFLUX 20.
OMIFLUX 20 contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

For long-term treatment:

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors like OMIFLUX 20 for at least three months. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of OMIFLUX 20. For patients expected to be on prolonged treatment or who take OMIFLUX 20 with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting OMIFLUX 20 treatment and periodically during treatment (see “INTERACTIONS”). OMIFLUX 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. OMIFLUX 20 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, when exceeding a treatment period of 1 year.

Effects on ability to drive and use machines:

OMIFLUX 20 may lead to drowsiness and impaired concentration. 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.

INTERACTIONS:

OMIFLUX 20 is metabolised via the hepatic cytochrome P450 enzyme system, which may affect the metabolism of other medicines metabolised by these enzymes when given concomitantly. The elimination of diazepam, warfarin and phenytoin may be prolonged when OMIFLUX 20 is given concomitantly. Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when OMIFLUX 20 is given concomitantly.

There is a possible interaction of OMIFLUX 20 with digoxin and a 10 % increase in digoxin bioavailability may be expected. Digoxin toxicity has been reported. Therapeutic monitoring of digoxin levels should be done. Caution should be exercised when OMIFLUX 20 is given at high doses in elderly patients.

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

Plasma concentrations of omeprazole and clarithromycin may be increased during concomitant administration. There is no interaction with metronidazole or amoxicillin.

Co-administration of OMIFLUX 20 with atazanavir/ritonavir resulted in a substantial reduction in atazanavir exposure (approximately 75 % decreased in AUC, C_{max} and C_{min}).

Concomitant administration of OMIFLUX 20 with nelfinavir is contraindicated (see "CONTRAINDICATIONS").

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

Concomitant administration of OMIFLUX 20 with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70 % for saquinavir in HIV-infected patients.

Concomitant administration of OMIFLUX 20 and tacrolimus may 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.

Concomitant administration of OMIFLUX 20 and methotrexate may increase serum levels of methotrexate, in high-dose methotrexate administration a temporary withdrawal of OMIFLUX 20 may need to be considered.

OMIFLUX 20 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 B12 absorption on long-term therapy.

OMIFLUX 20 is a CYP2C19 inhibitor. Concomitant administration of OMIFLUX 20 and CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. OMIFLUX 20 increased voriconazole C_{max} and AUC by 15 % and 41 %, respectively. A dose adjustment of omeprazole is not regularly required in either of these situations. However, a dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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 the rate of metabolism of OMIFLUX 20.
In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days.
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. Concomitant use of omeprazole and clopidogrel should be avoided (see "WARNINGS AND SPECIAL PRECAUTIONS").
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.
OMIFLUX 20, given in doses of 40 mg to healthy patients 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.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see "CONTRAINDICATIONS").

DOSAGE AND DIRECTIONS FOR USE:

OMIFLUX 20 is recommended to be given in the morning and swallowed whole with a half glass of liquid.
The contents of the OMIFLUX 20 capsules should not be chewed or crushed.
The recommended dosage for adults is: 20 mg once daily.
OMIFLUX 20 has a maximum daily dose of 20 mg.
Do not use continuously for more than 14 days without consulting a doctor.

Elderly:

Dose reductions are not necessary in elderly patients.

Impaired renal function:

Dose reductions are not necessary in renal impairment.

Impaired hepatic function:

Bioavailability and plasma half-life of OMIFLUX 20 are increased in patients with impaired hepatic function.

The long-term safety of OMIFLUX 20 in patients with renal and hepatic impairment has not been established (see “WARNINGS AND SPECIAL PRECAUTIONS”).

SIDE EFFECTS:

Blood and the lymphatic system disorders:

Less frequent: Pancytopenia, thrombocytopenia, agranulocytosis and leucopenia.

Immune system disorders:

Less frequent: *Hypersensitivity reactions:* Hypersensitivity with anaphylaxis and fever, angioedema, bronchospasms and anaphylactic shock.

Endocrine disorders:

Less frequent: Hyponatraemia, hypomagnesaemia and hypocalcaemia.

Nervous system disorders:

Frequent: Headache (severe enough to require discontinuation of therapy in some cases), vertigo and dizziness, somnolence and insomnia.

Less frequent: Paraesthesia, reversible mental confusion, aggression, hallucinations, agitation and depression.

Eye disorders:

Less frequent: Blurred vision.

Cardiac 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 cases), constipation, nausea, vomiting, flatulence and abdominal pain or colic.

Less frequent: Taste disturbances, benign reversible gastric glandular cysts, dry mouth, stomatitis, oesophageal candidiasis, acid regurgitation and increased gastro-intestinal bacteria.

Hepato-biliary disorders:

Frequent: Raised liver enzymes.

Less frequent: Hepatitis with or without jaundice and hepatic encephalopathy, hepatic failure.

Skin and subcutaneous tissue disorders:

Less frequent: Photosensitivity, bullous eruption, erythema multiforme, pruritus, dermatitis, urticaria, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome and alopecia.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Asthenia, arthralgia and myalgia.

Renal and urinary disorders:

Less frequent: Interstitial nephritis.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia, impotence.

General disorders and administration site conditions:

Less frequent: Malaise, fever, increased sweating.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Blurred vision, confusion, diaphoresis, flushing, headache, malaise, nausea, apathy, depression and tachycardia have been reported from overdosage 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 a consultation with a medical practitioner/doctor.

IDENTIFICATION:

OMIFLUX 20 is a white capsule filled with almost white to light brown pellets.

PRESENTATION:

OMIFLUX 20 is packaged in HDPE plastic bottles with polypropylene screw caps with induction heat seal liner or CRC polypropylene screw caps with induction heat seal liner and 1 g silica gel capsules or in aluminium blisters.

STORAGE INSTRUCTIONS:

Do not store above 25 °C. Store in the original packaging in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

43/11.4.3/0457

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

DATE OF PUBLICATION:

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[1]Company Reg. No.: 1990/001979/07