SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

LOKIT OTC, 20 mg hard gelatine capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOKIT OTC: Each hard gelatine capsule contains 20 mg omeprazole.

Contains sugar (sucrose 80,02 mg per capsule).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatine capsules

LOKIT OTC: Capsules of hard gelatine, number 2, with an opaque blue cap and opaque orange body. The capsules have been marked using white ink with the letter “O” in the cap and the number “20” in the body. The capsules are filled with white to beige micropellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOKIT OTC is indicated for the temporary, short-term relief of heartburn and hyperacidity.

4.2 Posology and method of administration

The maximum daily dose is 20 milligrams.

The maximum treatment period is 14 days.

If symptom control has not been achieved after 2 weeks of treatment with 20 mg daily, further investigation is recommended.

Elderly:

No dose adjustment is necessary in the elderly.

Impaired renal function:

Dose reductions are not necessary in renal impairment.

Impaired hepatic function:

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

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

Method of administration

For oral administration.

LOKIT OTC is recommended to be taken in the morning and swallowed whole with a half glass of liquid. The capsule should not be chewed or crushed.

4.3 Contraindications

LOKIT OTC is contraindicated in patients with hypersensitivity to omeprazole or to any of the excipients listed in 6.1.

LOKIT OTC must not be used concomitantly with nelfinavir (see section 4.5).

Safety in pregnancy and lactation has not been established.

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.

Co-administration of atazanavir with LOKIT OTC is not recommended (see section 4.5). If the combination of atazanavir with LOKIT OTC 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; LOKIT OTC should not be exceeded.

LOKIT OTC may reduce the absorption of vitamin B12 (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.

LOKIT OTC is a CYP2C19 inhibitor. When starting or ending treatment with LOKIT OTC, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and LOKIT OTC (see section 4.3). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of LOKIT OTC and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors PPIs such as LOKIT OTC 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 dysrhythmia can occur. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of LOKIT OTC.

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

Proton pump inhibitors such as LOKIT OTC, 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.

Subacute cutaneous lupus erythematosus

Proton pump inhibitors such as LOKIT OTC are associated with very infrequent cases of subacute cutaneous lupus erythematosus (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 healthcare professional should consider stopping LOKIT OTC. SCLE after previous treatment with a proton pump inhibitor 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, LOKIT OTC 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 LOKIT OTC treatment.

Clostridium difficile-associated diarrhoea:

Proton pump inhibitors including LOKIT OTC, may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea (CDAD). This diagnosis should be considered for diarrhoea that does not improve.

Treatment with LOKIT OTC may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

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

Paediatric population

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

LOKIT OTC contains sucrose and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take LOKIT OTC.

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 LOKIT OTC might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir:

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with LOKIT OTC. Concomitant administration of LOKIT OTC with nelfinavir is contraindicated (see section 4.3). Co-administration of omeprazole as in LOKIT OTC (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 LOKIT OTC with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole as in LOKIT OTC (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 LOKIT OTC on atazanavir exposure. The co-administration of LOKIT OTC (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.

Digoxin:

Simultaneous treatment with omeprazole as in LOKIT OTC and digoxin in healthy subjects lead to a 10 % increase in the bioavailability of digoxin as a consequence of the increased intragastric pH. Digoxin toxicity has been reported. However caution should be exercised when LOKIT OTC is given at high doses in elderly patients. Therapeutic medicine monitoring of digoxin should be then be reinforced.

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 as in LOKIT OTC (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46 % and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16 %.

Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole as in LOKIT OTC in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of LOKIT OTC and clopidogrel should be discouraged (see section 4.4).

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:

LOKIT OTC 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 and phenytoin serum levels is recommended and a reduction of warfarin and phenytoin dosage may be necessary when LOKIT OTC is given concomitantly.

Cilostazol:

LOKIT OTC, 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 LOKIT OTC treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism:

Saquinavir:

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70 % for saquinavir associated with good tolerability in HIV-infected patients.

Methotrexate:

When given together with proton-pump inhibitors such as LOKIT OTC, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of LOKIT OTC may need to be considered.

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.

Effects of other active substances on the pharmacokinetics of omeprazole:

Inhibitors 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. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

Breastfeeding

Safety in lactation has not been established (see section 4.3). LOKIT OTC is excreted in breast milk.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

LOKIT OTC may affect the ability to drive or use machines. Side effects such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

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

b. Tabulated list of adverse reactions

MedDra SOC/frequency	**Adverse reaction**
Infections and infestations	
Frequency unknown	*Clostridium difficile*-associated diarrhoea
Blood and the lymphatic system disorders	
Less frequent	Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders	
Less frequent	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition 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, depression and hallucinations, insomnia
Nervous system disorders	
Frequent	Headache
Less frequent	Dizziness, somnolence, paraesthesia, taste disturbance
Eye disorders	
Less frequent	Blurred vision
Ear and labyrinth disorders	
Less frequent	Vertigo
Vascular disorders	
Less frequent	Peripheral oedema
Respiratory, thoracic and mediastinal disorders	
Less frequent	Bronchospasm
Gastrointestinal disorders	
Frequent	Diarrhoea, constipation, abdominal pain or colic, nausea, vomiting, flatulence, fundic gland polyps (benign)
Less frequent	Dry mouth, stomatitis, oesophageal candidiasis, gastrointestinal candidiasis
Frequency unknown	Microscopic colitis
Hepato-biliary disorders	

Less frequent	Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy in patients with pre-existing liver disease, hepatic failure
Skin and subcutaneous tissue disorders	
Less frequent	Dermatitis, rash, urticaria, pruritus, photosensitivity, bullous eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, alopecia, erythema multiforme
Frequency unknown	Subacute cutaneous lupus erythematosus
Musculoskeletal, connective tissue and bone disorders	
Less frequent	Asthenia, arthralgia, myalgia, fracture of the hip, wrist or spine, muscular weakness, myopathy
Renal and urinary disorders	
Less frequent	Interstitial nephritis
Reproductive system and breast disorders	
Less frequent	Gynaecomastia
General disorders and administrative site conditions	
Less frequent	Malaise, peripheral oedema, increased sweating

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Single oral doses of up to 400 mg of LOKIT OTC have resulted in throbbing headache, drowsiness, tachycardia, flushing, blurred vision and dry mouth. Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Single cases of apathy, depression and confusion have been described.

There is no specific antidote for LOKIT OTC. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 11.4.3 – Medicines acting on the gastrointestinal tract.

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.

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 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.

5.2 Pharmacokinetic properties

Absorption:

Omeprazole is acid labile and is administered orally as enteric-coated granules in capsules. Absorption takes place in the small intestine and is usually completed within three to six hours. The systemic bioavailability of omeprazole from a single oral dose of LOKIT OTC is approximately 35 %. 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. Concomitant intake of food has no influence on the bioavailability. Omeprazole is 95 % bound to plasma proteins.

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 sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic 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.

Elimination:

The average half-life of the terminal phase of the plasma concentration-time curve is approximately forty minutes. There is no change in half-life during treatment. Almost 80 % of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-linearity:

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a nonlinear 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 sulfone).

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

Special populations

Hepatic impairment

As bioavailability and plasma half-life of omeprazole are increased in patients with impaired hepatic function a daily dose of 20 mg is generally sufficient. The long-term safety of LOKIT OTC in patients with hepatic impairment has not been established.

Renal impairment

The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function. No dose adjustment is required in patients with impaired renal function.

Elderly

The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 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

Content

Hypromellose

Methacrylic acid-ethyl acrylate Copolymer

Povidone

Sodium hydroxide (for pH-adjustment)

Sodium Lauryl Sulphate

Sodium Starch Glycolate

Sugar spheres (sucrose and corn starch)

Talc

Titanium dioxide

Triethyl citrate

Trisodium phosphate

Capsule shell

Gelatine

Eritrosine (E-127)

Indigo carmine (E-132)

Quinoleine yellow (E-104)

Red Iron Oxide (E-172)

Titanium dioxide (E1-171)

Water

Printing ink

Ethyl Alcohol anhydrous

Isopropyl Alcohol

N-Butyl Alcohol

Polyvinylpyrrolidone

Propylene Glycol

Shellac

Sodium Hydroxide

Titanium Dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Store in original package.

6.5 Nature and contents of container

LOKIT OTC hard gelatine capsules are packaged in blisters that are composed of:

- Hard aluminum sheet of 20 µm + heat-seal lacquer to PVC or PVDC and Polymide sheet of 25 µm + aluminum of 45 µm + PVC of 60 µm.

LOKIT OTC hard gelatine capsules are packaged in:

- White high-density polyethylene bottle with a white polypropylene cap provided with a compartment for silica gel desiccant.

The pack sizes available are 7, 14 capsules.

LOKIT OTC capsules is packaged in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBER

Lokit OTC: 54/11.4.3/0021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 October 2021

10. DATE OF REVISION OF THE TEXT