**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS:**

**S4**

**1. NAME OF THE MEDICINE:**

LOKIT OD 20, 20 mg hard gelatine capsules

LOKIT OD 40, 40 mg hard gelatine capsules

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION:**

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

LOKIT OD 40: Each hard gelatine capsule contains 40 mg omeprazole.

*Excipient with known effect*:

LOKIT OD 20 contains sugar (sucrose 80,02 mg per capsule) and LOKIT OD 40 contains sugar (sucrose 160,05 mg per capsule).

For the full list of excipients, see **section 6.1**.

**3. PHARMACEUTICAL FORM:**

Hard gelatine capsules

LOKIT OD 20: 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 micro pellets.

LOKIT OD 40: Capsules of hard gelatine, number 0, with an opaque blue cap and opaque orange body. The capsule has been marked using white ink with the letter “O” in the cap and the number “40” in the body. The capsules are filled with white to beige micro pellets.

## 4. CLINICAL PARTICULARS:

### 4.1 Therapeutic indications:

LOKIT OD is indicated in:

- Treatment of duodenal ulcer, gastric ulcer, reflux oesophagitis and Zollinger-Ellison syndrome and for the symptomatic relief of heartburn in patients with gastro-oesophageal reflux disease.
- *Helicobacter pylori*-positive duodenal ulcers as part of an eradication programme with appropriate antibiotics.

### 4.2 Posology and method of administration:

**Duodenal ulcer:**

The recommended dosage is 20 mg LOKIT OD 20 once daily for two to four weeks.

In some duodenal ulcer patient’s refractory to other treatment regimens, 40 mg LOKIT OD 40 once daily may be effective.

LOKIT OD 20 is indicated for *H.pylori*-positive duodenal ulcers, as part of the eradication programme with appropriate antibiotics.

**Gastric ulcer and reflux oesophagitis:**

The recommended dosage is 20 mg once daily for 4 to 8 weeks.

In some patients with gastric ulcer or reflux oesophagitis refractory to other treatment regimens, 40 mg LOKIT OD once daily may be effective.

In patients with severe or symptomatic recurrent reflux oesophagitis treatment can be continued with LOKIT OD as dosage of 20 mg once daily.

**Symptomatic gastro-oesophageal reflux disease:**

The recommended dosage is 20 mg LOKIT OD daily.

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

**Zollinger-Ellison syndrome:**

The recommended initial dosage is 60 mg LOKIT OD once daily. The dosage should be adjusted individually and treatment continued as long as is indicated.

Patients with severe disease have been effectively controlled on LOKIT OD 20 with more than 90 % maintained on doses of 20 mg to 120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

**Children:**

There is no experience with LOKIT OD in children.

**Elderly:**

No dose adjustment is necessary in the elderly.

**Impaired Renal Function:**

No dose adjustment is required in patients with impaired renal function.

**Impaired Hepatic Function:**

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 OD in patients with renal and hepatic impairment has not been established.

**Method of administration:**

For oral administration.

**4.3 Contraindications:**

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

LOKIT OD 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 OD is not recommended (see **section 4.5**). If the combination of atazanavir with LOKIT OD 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 OD 20 mg should not be exceeded.

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

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) such as LOKIT OD 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 OD.

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

Proton pump inhibitors, such as LOKIT OD, 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 OD, 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 OD. SCLE after previous treatment with LOKIT OD 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 OD 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 OD treatment.

*Clostridium difficile*-associated diarrhoea:

Proton pump inhibitors including LOKIT OD, 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 OD 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 OD in children.

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

**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 OD 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 OD.

Concomitant administration of omeprazole as in LOKIT OD with nelfinavir is contraindicated (see **section 4.3**). Co-administration of LOKIT OD (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 OD with atazanavir is not recommended (see **section 4.4**). Concomitant administration of omeprazole as in LOKIT OD (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 as in LOKIT OD on atazanavir exposure. The co-administration of omeprazole as in LOKIT OD (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 OD 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 OD is given at high doses in elderly patients. Therapeutic medicine monitoring of digoxin should 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 OD (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 OD in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of LOKIT OD 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 OD 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 patients receiving warfarin and phenytoin is recommended and a reduction of warfarin and phenytoin dose may be necessary.

*Cilostazol:*

**LOKIT OD**, 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 OD 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 associate with good tolerability in HIV-infected patients.

*Methotrexate:*

When given together with proton-pump inhibitors such as LOKIT OD, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of LOKIT OD 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 breastfeeding has not been established (see **section 4.3**). LOKIT OD 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 OD 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 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 and connective tissue 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 administration 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 OD 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 antidote for overdose with LOKIT OD. 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 OD 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*:**

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 OD 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)

Quinoline yellow (E-104)

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 OD 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 OD 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, 28 or 30 capsules.

LOKIT OD capsules are packaged in an outer cardboard carton.

Not all pack sizes may be marketed.

**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 OD 20:54/11.4.3/0022

LOKIT OD 40: 54/11.4.3/0023

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:**

12 October 2021

**10. DATE OF REVISION OF THE TEXT:**