SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Lokit-20 (Omeprazole Capsules 20mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredient	Pharma-copoeial Reference	Pharmaceutical Function	Qty. Per /capsule (mg)
1	Omeprazole enteric coated pellets (8.5%)#	BP	Active	A*
2	Maroon / Flesh Pink Size 2, Plain Empty Hard Gelatin Capsules	IH	Unit Dose Holder	01

#: Omeprazole pellets of 3% overage (i.e. 7.06 mg) is added per capsule

* Considering Omeprazole pellets of 8.5% strength, quantity required to achieve label claim of 20mg is = 20 x 100 = 235.29 mg
8.5

Including 3% overages we get = 235.29 + 7.06 = 242.35 mg

Fill weight per capsule (A) =

$$\frac{242.35 \quad X \quad 100}{P}$$

Where P is the potency of the incoming Omeprazole pellets.
If P is more than 100 % (With respect to label claim) for calculations it is to be taken as 100 only.
Weight of filled capsule (B) = (A + 63) mg

Where 63mg is the approximate weight of Size '2' empty gelatin capsules.

3. PHARMACEUTICAL FORM

Capsule

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LOKIT is indicated for the treatment of Treatment of Reflux Oesophagitis, Duodenal ulcer, Benign gastric ulcer, Prophylaxis of acid aspiration,

Dyspeptic symptoms (e.g. heartburn), Zollinger Ellison Syndrome and other pathological hypersecretory states, Heliobacter pylori eradication (in combination with antibiotics).

4.2 Posology and method of administration

FOR ADULTS:

Reflux oesophagitis : 20 mg once daily for 4 weeks. Duodenal ulcer : 20 mg once daily for 2 weeks.

Gastric ulcer : 20 mg once daily for 4 weeks.

Zollinger Ellison Syndrome : 60 mg once daily till clinically required.

Heliobacter pylori eradication: 40mg twice daily in association with antimicrobial agents.

FOR CHILDREN:

For body weight of 10-20 kg, the dose of Omeprazole is 10 mg once daily. For body weight of > 20 kg the dose of Omeprazole is 20 mg once daily.

For patients who do not experience relief during prescribed period further course of 2 weeks may be given.

No dose adjustment is required in the elderly and in patients with reduced renal function. Due to an increase in the bioavailability plasma half-life of omeprazole in patients with impaired hepatic function a daily dose of 20 mg is generally adequate.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles

Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir

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 proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor 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, 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 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. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole 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 PPI.

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

Proton pump inhibitors, 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 10-40%. 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 (SCLE)

Proton pump inhibitors are 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 Losec. 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, omeprazole 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 proton pump inhibitor treatment.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Losec contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile* .

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

4.5 Interaction with other medicinal products 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.

Nelfinavir, atazanavir

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated. 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 –90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). 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.

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 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 (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 in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

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

Omeprazole 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 drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax 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 omeprazole 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.

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.

Methotrexate

When given together with proton-pump inhibitors, 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

omeprazole 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.

4.6 Pregnancy and lactation:

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

4.7 Effects on ability to drive and use machines

Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur.

4.8 Undesirable effects

Omeprazole is well tolerated. Headache, diarrhea, abdominal pain, nausea, dizziness, vomiting and flatulence have been reported but are rare. Skin rash has occurred in few patients.

4.9 Overdose

Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases.The symptoms described in connection to omeprazole overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with increased dose and no specific treatment has been needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton Pump Inhibitor

ATC code: A02BC01

Mechanism of action

Omeprazole, a substituted benzimidazole, is a selective proton pump inhibitor (which inhibits directly and in dose-dependent fashion the H+/K+-ATPase of the parietal cells of the stomach responsible for gastric acid secretion. By this selective intracellular attack, independently from membrane located receptors like histamine H2-, muscarine M1- or gastrineric receptors, omeprazole belongs to an independent class of inhibitors which block the terminal secretion process. By its mode of action, omeprazole reduces not only basal but also stimulus- induced acid secretion, independently of the kind of stimulus. Omeprazole thus increases the pH-value and reduces the secretory volume.

Microbiology (when applicable)

Not Applicable

Drug resistance (when applicable)

Not Applicable

Cross resistance (when applicable)

Not Applicable

Pharmacodynamic effects

Omeprazole, a substituted benzimidazole, is a selective proton pump inhibitor (which inhibits directly and in dose-dependent fashion the H+/K+-ATPase of the parietal cells of the stomach responsible for gastric acid secretion. By this selective intracellular attack, independently from membrane located receptors like histamine H2-, muscarine M1- or gastrineric receptors, omeprazole belongs to an independent class of inhibitors which block the terminal secretion process. By its mode of action, omeprazole reduces not only basal but also stimulus- induced acid secretion, independently of the kind of stimulus. Omeprazole thus increases the pH-value and reduces the secretory volume.

Oral dosing with 20 mg omeprazole once daily produces inhibition of gastric acid secretion within 1-2 hours of the first dose. The maximum effect is achieved within 4 days of starting treatment after which the degree of inhibition remains constant. The mean decrease in pentagastrin-stimulated peak acid output twenty-four hours after dosing is about 70%.

Helicobacter pylori (*Hp*) is associated with acid peptic disease including duodenal ulcer (DU) and gastric ulcer (GU) in which about 95% and 80% of patients respectively are infected with this bacterium. *Hp* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between *Hp* and gastric carcinoma.

Omeprazole has been shown to have a bactericidal effect on Hp *in vitro.* Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

5.2 Pharmacokinetic properties

Absorption

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets.

Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. 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. Omeprazole is 97% plasma protein bound.

Metabolism

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

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive

metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Excretion

The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. 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.

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear 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 sulphone). No metabolite has been found to have any effect on gastric acid secretion.

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maroon / Flesh Pink Size 2, Plain Empty Hard Gelatin Capsules

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months (3 Years)

6.4 Special precautions for storage

Store below 30ºC in a dry place. Protect from light.

6.5 Nature and contents of container

ALU/ALU Strip

6.6 Instructions for use and handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

KOPRAN LTD.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

KOP/IND/009
04333/06825/REN/2018

9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION

7/05/2009

Mar 14, 2019

10. DATE OF REVISION OF THE TEXT