Summary of Product Characteristics

1. Name of the Medicinal Product

SURE KIT Tablets.

2. Qualitative and quantitative composition

Each Kit Contains

A. Lansoprazole Delayed Release Capsule BP
30 mg Each hard gelatin capsule contains Lansoprazole BP 30 mg
For a full list of excipients, see section 6.1.

B. Tinidazole Tablets 500 mg

Each Film Coated Tablet Contains
Tinindazole BP .....500 mg

For a full list of excipients, see section 6.1.

C. Clarithromycin Tablets BP 250 mg Each Film Coated Tablet Contains
Clarithromycin BP..... 250 mg
For a full list of excipients, see section 6.1.

3. Pharmaceutical form:

Tablet and capsule for oral use

4. Clinical Particulars

4.1 Therapeutic indications and uses:

SURE KIT is indicated for the eradication of H. pylori in active chronic gastritis, duodenal and gastric ulcers.

4.2 Posology and method of administration:

One SURE KIT pack contains two capsules of lansoprazole (30 mg), two tablets of tinidazole (500 mg) and two tablets of clarithromycin (250 mg). One pack is for 1 day of treatment. From this specially designed pack, one capsule of lansoprazole, one tablet of tinidazole and one tablet of clarithromycin is to be taken in the morning and similarly one each in the evening. The duration of therapy recommended is for 7 days.

Renal and Hepatic Impairment

Caution should be exercised while administering SURE KIT to patients with renal and hepatic impairment.

Method of administration

For oral administration.

Section 4.3 Contraindications:

1. Hypersensitivity to lansoprazole or tinidazole or clarithromycin.
2. Lansoprazole should not be administered with atazanavir.
3. During the first trimester of pregnancy.In Nursing Mothers: Interruption of breastfeeding is recommended during tinidazole therapy and for 3 days following the last dose.
4. Concomitant Administration of Clarithromycin and Cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine. There have been postmarketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, astemizole or terfenadine, resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes), most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

4.4 Special warnings and precautions for use:
Clarithromycin
General Prescribing clarithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Clarithromycin is principally excreted via the liver and kidneys. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without co- existing hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate. Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 mL/min.

Tinidazole

Neurological Adverse Reactions

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with tinidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of tinidazole therapy. Vaginal Candidiasis The use of tinidazole may result in Candida vaginitis.

Blood Dyscrasia

Tinidazole should be used with caution in patients with evidence of or history of blood dyscrasia. **Lansoprazole**
Gastric Malignancy Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.
Clostridium difficile-associated Diarrhea
Published observational studies suggest that PPI therapy as with lansoprazole may be associated with an increased risk of C. difficile-associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. CDAD has been reported with use of nearly all antibacterial agents.

4.5 Interactions with other medicinal products and other forms of interaction.

Lansoprazole

Drugs with pH-Dependent Absorption Kinetics

Lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor, atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole and other PPIs should not be co-administered with atazanavir. Lansoprazole and other PPIs may interfere with the absorption of other drugs where the gastric pH is an important determinant of oral bioavailability (e.g. ampicillin esters, digoxin, iron salts, ketoconazole).

Warfarin

In a study of healthy subjects, co-administration of single or multiple 60 mg doses of lansoprazole and warfarin did not affect the pharmacokinetics of warfarin nor prothrombin time. However, there have been reports of increased international normalized ratio (INR) and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in the INR and prothrombin time may lead to abnormal bleeding and, even, death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in the INR and prothrombin time.

Tacrolimus

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

4.6 Pregnancy and lactation:

Lansoprazole, Tinidazole, Clarithromycin

There are no well-controlled studies of lansoprazole or tinidazole or clarithromycin in pregnant women. Clarithromycin is not indicated during pregnancy; hence, this combination is not indicated in pregnancy.

Lactation

Lansoprazole, Tinidazole, Clarithromycin

There are no well-controlled studies of the use of lansoprazole or tinidazole or clarithromycin during lactation. Tinidazole is excreted in breast milk in concentrations similar to those seen in serum. Since some components of SURE KIT are excreted in breast milk, and risk of
potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, caution should be exercised when administering this kit to a nursing mother.

4.7 Effects on ability to drive and use machines:

No effect on concentration and co-ordination.

4.8 Undesirable effects:

Lansoprazole

Adverse reactions are presented by System Organ Class (SOC) and frequency. Frequencies are defined as follows: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Blood and lymphatic system disorders	—	—	—	Leukopenia*, thrombocytopenia*, anaemia	Pancytopenia*, agranulocytosis*, eosinophilia
Immune system disorders	—	—	—	Anaphylactic shock*	—
Metabolism and nutritional disorders	—	—	—	Hyponatraemia*, hypomagnesaemia*‡, hypocalcaemia*, hypokalaemia*	—
Psychiatric disorders	Depression	Hallucination, insomnia, confusion	—	—	Visual hallucinations
Nervous system disorders	Headache, dizziness	Paraesthesia, vertigo, restlessness, somnole	—	—	—

		nce, tremor			
Eye disorders	Visual disturbances	—	—	—	—
Gastrointestinal disorders	Vomiting, nausea, diarrhoea, stomachache, constipation, flatulence, dry mouth or throat, fundic gland polyps (benign)	—	Pancreatitis, candidiasis of the oesophagus	Glossitis, taste disturbances	Colitis*‡, stomatitis
Hepatobiliary disorders	Increase in liver enzyme levels	—	—	Hepatitis, jaundice	—
Skin and subcutaneous tissue disorders	Urticaria, itching, rash	—	Petechiae, purpura, erythema multiforme, photosensitivity, hair loss	Stevens-Johnson syndrome*‡, toxic epidermal necrolysis*‡	Subacute cutaneous lupus erythematosus*‡, drug reaction with eosinophilia and systemic symptoms (DRESS)*‡
Musculoskeletal and connective tissue disorders	—	Fracture of the hip, wrist or spine‡, arthralgia, myalgia	—	—	—
Renal and urinary disorders	—	—	Tubulointerstitial nephritis (with possible progression to renal failure)	—	—
Reproductive system and breast disorders	—	—	—	Gynaecomastia	—

General disorders and administration site conditions	Fatigue	Oedema	—	—	Angioedema, fever, hyperhidrosis, anorexia, impotence
Investigations	—	Increase in cholesterol and triglyceride levels	—	—	—

Notes:
* Post-marketing events.
‡ Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia.

Tinidazole

Reported adverse reactions have generally been infrequent, mild and self-limiting. The undesirable effects are presented below according to MedDRA System Organ Class (SOC) and frequency. Within each frequency category, adverse drug reactions (ADRs) are presented in order of clinical importance.

Frequency categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (frequency cannot be estimated from available data).

System Organ Class	Common	Not Known
Blood and lymphatic system disorders	Leukopenia	—
Immune system disorders	—	Drug hypersensitivity
Metabolism and nutrition disorders	Decreased appetite	—
Nervous system disorders	Headache	Convulsions, peripheral neuropathy, paraesthesia, hypoaesthesia, sensory disturbances, ataxia, dizziness, dysgeusia
Ear and labyrinth disorders	—	Vertigo
Vascular disorders	—	Flushing
Gastrointestinal disorders	Vomiting, diarrhoea, nausea, abdominal pain	Glossitis, stomatitis, tongue discolouration
Skin and subcutaneous tissue disorders	Allergic dermatitis	Pruritus, angioedema, urticaria
Renal and urinary disorders	—	Chromaturia
General disorders and administration site conditions	—	Pyrexia, fatigue

Clarithromycin

a. Summary of the Safety Profile

The most frequent and common adverse reactions associated with clarithromycin therapy in both adults and paediatric patients are **abdominal pain, diarrhoea, nausea, vomiting and taste perversion**. These reactions are generally mild in intensity and are consistent with the established safety profile of macrolide antibiotics. No significant difference was observed in clinical trials in the incidence of gastrointestinal adverse reactions between patients with and without pre-existing mycobacterial infections.

b. Tabulated Summary of Adverse Reactions

Adverse reactions considered at least possibly related to clarithromycin are presented by System Organ Class (SOC) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and not known (cannot be estimated from available data). The available table reports common, uncommon and not-known reactions; no very common reactions are specifically identified.

System Organ Class	Common	Uncommon	Not Known*
Infections and infestations	—	Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system disorders	—	Leukopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders	—	Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders	—	Anorexia, decreased appetite	—
Psychiatric disorders	—	Insomnia	Anxiety, nervousness[3], screaming[3], psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams
Nervous system disorders	Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[6], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders	—	Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders	—	Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT	Torsades de pointes[7], ventricular tachycardia[7]

		prolonged[7], extrasystoles[1], palpitations	
Vascular disorders	—	Vasodilation[1]	Haemorrhage[8]
Respiratory, thoracic and mediastinal disorders	—	Asthma[1], epistaxis[2], pulmonary embolism[1]	—
Gastrointestinal disorders	Diarrhoea[9], vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence	Acute pancreatitis, tongue discolouration, tooth discolouration
Hepatobiliary disorders	—	Abnormal liver function test	Cholestasis[4], hepatitis[4], increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyl transferase[4], hepatic failure[10], jaundice, hepatocellular injury
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	Bullous dermatitis[1], pruritus, maculopapular rash[3]	Stevens-Johnson syndrome[5], toxic epidermal necrolysis[5], drug reaction with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	—	Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2],[11]**, myopathy
Renal and urinary disorders	—	Increased blood creatinine[1], increased blood urea[1]	Renal failure, interstitial nephritis
General disorders and administration site conditions	—	Injection-site phlebitis[1], injection-site pain[1], injection-site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]
Investigations	—	Abnormal albumin/globulin ratio[1], increased blood alkaline phosphatase[4], increased blood lactate dehydrogenase[4]	Increased international normalised ratio[8], prolonged prothrombin time[8], abnormal urine colour[1]

Notes:

[1] Adverse reactions reported only for the **powder for solution for injection** formulation.

[2] Adverse reactions reported only for the **extended-release tablets**

formulation.
[3] Adverse reactions reported only for the **granules for oral suspension** formulation.
[4] Adverse reactions reported only for the **immediate-release tablets** formulation.
[5], [7], [9], [10] Refer to the corresponding descriptions in the product information.
[6], [8], [11] Refer to the corresponding descriptions of selected adverse reactions.
* Post-marketing adverse reactions reported voluntarily from a population of uncertain size; therefore, their frequency cannot be reliably estimated or a causal relationship with clarithromycin exposure established.
** In some reports of rhabdomyolysis, clarithromycin was administered concomitantly with medicines known to be associated with rhabdomyolysis, including statins, fibrates, colchicine or allopurinol.

c. Description of Selected Adverse Reactions

Injection-site reactions: Injection-site phlebitis, injection-site pain, vessel puncture-site pain and injection-site inflammation are specific to the intravenous formulation of clarithromycin.

Rhabdomyolysis: In some reports, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol; therefore, concomitant use should be considered when evaluating the risk of rhabdomyolysis.

Central nervous system effects and drug interactions: Post-marketing reports have described drug interactions and CNS effects, including somnolence and confusion, with concomitant clarithromycin and triazolam use. Patients should therefore be monitored for increased CNS pharmacological effects.

Extended-release tablet residues: Rare reports of clarithromycin extended-release tablets being observed in the stool have been described, particularly in patients with anatomical or functional gastrointestinal disorders associated with shortened gastrointestinal transit time. Tablet residues have also been reported in association with diarrhoea. Patients experiencing tablet residues in the stool together with lack of clinical improvement should be switched to another clarithromycin formulation, such as an oral suspension, or to an alternative antibiotic.

d. Paediatric Population

Clinical trials have evaluated clarithromycin paediatric suspension in children aged **6 months to 12 years**. Accordingly, children below 12 years should use the paediatric suspension formulation. There are insufficient data to recommend a dosage regimen for intravenous clarithromycin in patients below 18 years of age. The **frequency, type and severity of adverse reactions in children are expected to be similar to those observed in adults**.

e. Immunocompromised Patients

In patients with AIDS or other immunocompromised conditions receiving high-dose clarithromycin for prolonged periods for mycobacterial infections, it may be difficult to distinguish adverse reactions attributable to clarithromycin from manifestations of underlying HIV disease or intercurrent illness.

In adults receiving total daily doses of **1,000 mg or 2,000 mg**, the most frequently reported adverse reactions were nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing

disturbance, and elevations in SGOT and SGPT. Less frequently reported events included dyspnoea, insomnia and dry mouth. The incidence was generally comparable between the 1,000 mg and 2,000 mg dosage groups, but adverse reactions were generally **3–4 times more frequent at a total daily dose of 4,000 mg**.

Laboratory abnormality	**Patients receiving 1,000–2,000 mg/day**
Seriously abnormal elevated SGOT/SGPT	Approximately 2–3%
Abnormally low white blood cell counts	Approximately 2–3%
Abnormally low platelet counts	Approximately 2–3%
Elevated blood urea nitrogen	Lower percentage of patients
Overall abnormalities at 4,000 mg/day	Slightly higher incidence across parameters, except white blood cell count

Laboratory abnormalities were assessed using values outside the specified extreme high or low limits. Patients receiving **4,000 mg/day** generally showed slightly higher incidences of abnormal laboratory values than those receiving 1,000–2,000 mg/day, except for white blood cell counts.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose:

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required.

5. Pharmacological Properties:

5.1 Pharmacodynamic properties:

Lansoprazole
Mechanism of Action
Lansoprazole is a gastric PPI. It inhibits the final stage of gastric acid formation by inhibiting the activity of H+/K+ ATPase of the parietal cells in the stomach. The inhibition is dosedependent and reversible and the effect applies to both basal and stimulated secretion of gastric acid.
Lansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulfhydryl group of H+/K+ATPase causing inhibition of the enzyme activity.

Antisecretory Activity

Lansoprazole is a selective inhibitor of the parietal cell proton pump. A single oral dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by about 80 %. After repeated daily administration for 7 days, about 90 % inhibition of gastric acid secretion is achieved. It has a corresponding effect on the basal secretion of gastric acid. A single oral dose of 30 mg reduces basal secretion by about 70 %, and the patients' symptoms are consequently relieved starting from the first dose. After 8 days of repeated administration, the reduction is about 85 %. A rapid relief of symptoms is obtained by one capsule (30 mg) daily and most patients with duodenal ulcer recover within 2

weeks, and patients with gastric ulcer and reflux esophagitis recover within 4 weeks. By reducing gastric acidity, lansoprazole creates an environment in which appropriate antibiotics can be effective against H. pylori.

Tinidazole

Tinidazole is an anti-protozoal, antibacterial agent. The nitro-group of tinidazole is reduced by cell extracts of *Trichomonas*. The free nitro-radical generated as a result of this reduction may be responsible for the anti-protozoal activity. Chemically reduced tinidazole was shown to release nitrites and cause damage to purified bacterial DNA *in-vitro*. Additionally, the drug caused DNA base changes in bacterial cells and DNA strand breakage in mammalian cells. The mechanism by which tinidazole exhibits activity against *Giardia* and *Entamoeba* species is not known.
Tinidazole is active against *H. pylori*, *Gardnerella vaginalis* and most anaerobic bacteria, including *Bacteroides fragilis, Bacteroides melaninogenicus, Bacteroides* spp., *Clostridium* spp., *Eubacterium* spp., *Fusobacterium* spp., *Peptococcus* spp., *P eptostreptococcus* spp. and *Veillonella* spp. *H. pylori* is associated with acid peptic disease, including duodenal ulcer and gastric ulcer, in which about 95% and 80% of patients, respectively, are infected with this agent. *H. pylori* is also implicated as a major contributing factor in the development of gastritis and ulcer recurrence in such patients. Evidence suggests a causative link between *H. pylori* and gastric carcinoma. Clinical evidence has shown that the combination of tinidazole with a PPI and clarithromycin eradicates 91 to 96% of *H. pylori* isolates. Various *H. pylori* eradication regimens have shown that eradication of *H. pylori* heals duodenal ulcers and reduces the risk of ulcer recurrence.

Clarithromycin

Clarithromycin is a semisynthetic derivative of erythromycin A. Clarithromycin is active invitro against a variety of aerobic and anaerobic Gram-positive and Gram-negative bacteria as well as most Mycobacterium avium complex (MAC) bacteria. Additionally, the 14-OHclarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OHclarithromycin is twice as active against Hemophilus influenzae microorganisms as the parent compound. However, for Mycobacterium avium

complex (MAC) isolates the 14-OH-metabolite is 4 to 7 times less active than clarithromycin. The clinical significance of this activity against Mycobacterium avium complex is unknown.
Clarithromycin has bactericidal activity against several bacterial strains. The organisms include Hemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H. pylori and Campylobacter spp.

5.2 Pharmacokinetic properties:

Lansoprazole

Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After single-dose administration of 15 mg to
60 mg of oral lansoprazole, the peak plasma concentrations (Cmax) of lansoprazole and the area under the plasma concentration curves (AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics is unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with the mean Cmax occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both the Cmax and AUC are diminished by about 50 to 70% if lansoprazole is given 30 minutes after food, compared with the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 mcg/mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl

and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species that inhibit acid secretion by blocking the proton pump at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Elimination

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Tinidazole

Absorption

After oral administration, tinidazole is rapidly and completely absorbed. A bioavailability study of tinidazole tablets was conducted in adult healthy volunteers. All subjects received a single oral dose of 2 g (four 500 mg tablets) of tinidazole following an overnight fast. Oral administration of four 500 mg tablets of tinidazole under fasted conditions produced a mean peak plasma concentration (Cmax) of 47.7 (±7.5) mcg/mL, with a mean time to peak concentration (Tmax) of 1.6 (±0.7) hours, and a mean area under the plasma concentration-time curve (AUC0-infinity) of 901.6 (± 126.5) mcg.hr/mL at 72 hours. The elimination half-life (T1/2)
was 13.2 (±1.4) hours. Mean plasma levels decreased to 14.3 mcg/mL at 24

hours, 3.8 mcg/mL at 48 hours, and 0.8 mcg/mL at 72 hours following administration. Steady-state conditions are reached in 21/2 to 3 days of multi-day dosing. Administration of tinidazole tablets with food resulted in a delay in the Tmax of approximately 2 hours and a decline in the Cmax of approximately 10%, compared with fasted conditions. However, administration of tinidazole with food did not affect AUC or T1/2 in this study. In healthy volunteers, administration of crushed tinidazole tablets in artificial

cherry syrup, after an overnight fast, had no effect on any pharmacokinetic parameter as compared with tablets swallowed whole under fasted conditions. ***Distribution***

Tinidazole is distributed into virtually all tissues and body fluids, and also crosses the bloodbrain barrier. The apparent volume of distribution is about 50 liters. Plasma protein binding of tinidazole is 12%. Tinidazole crosses the placental barrier and is secreted in breast milk.

Metabolism

Tinidazole is significantly metabolized in humans prior to excretion. Tinidazole is partly metabolized by oxidation, hydroxylation and conjugation. Tinidazole is the major drug-related constituent in plasma after human treatment, along with a small amount of the 2-hydroxymethyl metabolite.

Tinidazole is biotransformed mainly by cytochrome (CY) P3A4. In an in vitro metabolic drug interaction study, tinidazole concentrations of up to 75 mcg/mL did not inhibit the enzyme activities of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.

The potential of tinidazole to induce the metabolism of other drugs has not been evaluated.

Elimination

The plasma half-life of tinidazole is approximately 12 to 14 hours. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20 to 25% of the administered dose). Approximately 12% of the drug is excreted in the feces.

Renal Impairment

The pharmacokinetics of tinidazole in patients with severe renal impairment (creatinine clearance

Hepatic Impairment

There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies.

Clarithromycin

Clarithromycin is absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH-clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC).

In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2 mcg/mL with a 250 mg dose administered every 12 hours, and 3 to 4 mcg/mL with a 500 mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours, but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a dosing of 250 mg every 12 hours, the principal metabolite, 14-OH-clarithromycin, attains a peak steadystate concentration of about 0.6 mcg/mL and has an elimination half-life of 5 to 6 hours. With a dosing of 500 mg every 8 to 12 hours, the peak steady-state concentration of 14-OHclarithromycin is slightly higher (up to 1 mcg/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days.

After a 250 mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5

mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH-clarithromycin, which accounts for an additional 10 to 15% of the dose with either a 250 mg or a 500 mg tablet administered every 12 hours.
Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500 mg or 1,000 mg doses of clarithromycin every 12 hours, the steady-state clarithromycin Cmax values ranged from 2 to 4 mcg/mL and 5 to 10 mcg/mL, respectively.

5.3 Preclinical safety data:

Lansoprazole Delayed-Release Capsules

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction or genotoxicity.
In two rat carcinogenicity studies, lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids associated with hypergastrinaemia due to inhibition of acid secretion.
Intestinal metaplasia was also observed, as were Leydig cell hyperplasia and benign Leydig cell tumours. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.
In mouse carcinogenicity studies dose-related gastric ECL cell hyperplasia developed as well as liver tumours and adenoma of rete testis.
The clinical relevance of these findings is unknown.

Tinidazole Tablets

Tnidazole has been shown to be mutagenic in some bacterial strains tested in vitro (with and without metabolic activation). Tinidazole was negative for mutagenicity in a mammalian cell culture system utilising Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the

Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for in vivo genotoxicity in the mouse micronucleus assay.

Clarithromycin Tablets:

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg).
In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.
Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Spraque-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from Clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities, which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels, which were clearly toxic to the mothers.

6. Pharmaceutical Properties

6.1 List of excipients:

Lansoprazole Delayed Release Capsule BP 30 mg

NA

Tinidazole Tablets 500 mg

Starch IP/BP/USP

Di Calcium Phosphate IP/BP/U

SP Doshion p-544 DS IP/USP

P.V.P.K-30 IP/BP/USP

Sodium benzoate IP/BP/USP

Magnesium Stearate IP/BP/USP Talcum IP/BP/USP

Sodium Starch Glycolate IP/BP/USP Aerosil (Cabosil) IP/BP/USP

Cross Carmalose Sodium IP/BP/U

SP Film Coat Colour Aq Tartrazine IHS

Clarithromycin Tablets BP 250 mg

Lactose IP/BP/USP

M.C.C Powder IP/BP/USP

Cross Carmalose Sodium IP/US

P P.V.P.K-30 IP/BP/USP

Sodium benzoate IP/BP/USP

Magnesium Stearate IP/BP/U

SP Cross Povidone XL-10 IP/BP/U

SP

Sodium Starch Glycolate IP/BP/USP Aerosil (Cabosil) IP/BP/USP

Talcum IP/BP/USP

Doshion p-544 DS IP/BP/U

SP Sodium Lauryl SulphateIP/BP/USP

Potassium Sorbate IP/BP/U

SP

Film Coat Titanium Dioxide IP/BP/USP

Methylene Di Chloride
IP/BP/US
P Iso Propyl Alcohol IP/BP/USP

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 Months

6.4 Special precautions for storage:

Store in cool & dry place. Protect from light.

6.5 Nature and contents of container:

1 Kit of 4 Tablets and 2 Capsules Contains:

2 Lansoprazole Delayed Release Capsule BP
30 mg 2 Tinidazole Tablets 500 mg
2 Clarithromycin Tablets BP 250 mg are packed in Aluminium Strips pack. Such 7 Kits are packed in a carton along with a pack insert.

6.6 Special precautions for disposal and other handling:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing Authorisation Holder:

NATIONAL PHARMACY LTD

Colchester Park,

P.O BOX 17843 – 00500

Nairobi -Kenya.

8. Marketing Authorisation Number(s)

H2010/24367/303/R1

9. Date of First Authorisation/Renewal of the Authorisation
03 July 2026

10. Date of Revision of the Text

24/08/2026