National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

BAYLOKIT

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Name of the Medicinal Product

Combipack of Lansoprazole Gastro Resistant Capsules, Clarithromycin Tablets & Tinidazole Tablets

Qualitative and Quantitative Composition

Each Kit Contains:

(A) 2 Lansoprazole capsule

Each Hard Gelatin capsule contains:

Lansoprazole USP 30 mg

(As enteric coated Granules)

Approved colour granules used for empty capsule shell.

(B) 2 Clarithromycin Tablets Each film coated tablets contains:

Clarithromycin USP 250 mg

Colour: Titanium Dioxide

(c) Tinidazole Tablets

Each film coated tablet contains:

Tinidazole USP 500 mg

Colour: Indigo Carmine Lake & Indigo Carmine Supra

Pharmaceutical Form

Tablet and capsule for oral use

Clinical Particulars Therapeutic Indications

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

Posology and Method of Administration

One BAYLOKIT 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 ImpairmentCaution should be exercised while administering BAYLOKIT KIT to patients with renal and hepatic impairment.

Method of administration

For oral administration.

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.

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 DyscrasiaTinidazole 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 DiarrheaPublished 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.

Interactions with Other Medicinal Product and Other Form 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.

Pregnancy and Lactation Pregnancy

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 BAYLOKIT 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.

Effect on Ability to Drive and use Machine

No effect on concentration and co-ordination.

Undesirable

Effects

Lansoprazole

Abdominal pain, Constipation, Diarrhea and Nausea

Tinidazole

Vascular Disorders: Flushing.General Disorders and Administration Site Conditions: Pyrexia, fatigue.Nervous System Disorders: Ataxia, convulsions (rarely), dizziness, headache, hypesthesia, paresthesia, neuropathy peripheral, sensory disturbances, dysgeusia. Ear and Labyrinth Disorders: Vertigo.Gastrointestinal Disorders: Abdominal pain, diarrhea, tongue discoloration, glossitis, nausea, stomatitis, vomiting. Metabolism and Nutrition Disorders: Decreased appetite.

Clarithromycin

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and dysgeusia Gastrointestinal Disorders: Diarrhea, vomiting, dyspepsia, nausea, abdominal pain. Hepatobiliary Disorders: Liver function test abnormal. Immune System Disorders: Anaphylactoid reaction. Infection and Infestations: Candidiasis. Nervous System Disorders: Dysgeusia, headache. Psychiatric Disorders: Insomnia.

Overdose

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

Pharmacological Properties

Pharmacodynamic Properties

Pharmacodynamics:

<u>Mechanism of Action</u>

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 dose-dependent 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.

Pharmacokinetic Properties

Pharmacokinetics

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 (C_{max}) 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 C_{max} 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 C_{max} 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 ^{14}C-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

Pharmacodynamics

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 Bacteroidesfragilis, Bacteroides melaninogenicus, Bacteroides spp., Clostridium spp., Eubacterium spp., Fusobacterium spp., Pep tococcus spp., Peptostreptococcus 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.

Pharmacokinetics

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 (C_{max}) of 47.7 (±7.5) mcg/mL, with a mean time to peak concentration (T_{max}) of 1.6 (±0.7) hours, and a mean area under the plasma concentration-time curve ($AUC_{0-infinity}$) of 901.6 (± 126.5) mcg.hr/mL at 72 hours. The elimination half-life (T½) 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 2½ to 3 days of multi-day dosing. Administration of tinidazole tablets with food resulted in a delay in the $T_{max}$of approximately 2 hours and a decline in the C_{max} of approximately 10%, compared with fasted conditions. However, administration of tinidazole with food did not affect AUC or $T_{½}$ 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 blood-brain 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 <22 mL/min) are not significantly different from the pharmacokinetics seen in healthy subjects. However, during hemodialysis, clearance of tinidazole is significantly

increased; the half-life is reduced from 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis has not been investigated.

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

Pharmacodynamics

Clarithromycin is a semisynthetic derivative of erythromycin A. Clarithromycin is active in-vitro 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-OH-clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH-clarithromycin 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.

Pharmacokinetics

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 steady-state 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-OH-clarithromycin 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 C_{max} values ranged from 2 to 4 mcg/mL and 5 to 10 mcg/mL, respectively.

Preclinical Safety Data

NA

Incompatibilities

Not applicable.

Shelf life

3 years from the date of manufacturing.

Do not use the product after the expiry of the shelf life.

Special Precautions for Storage

Store in a dry place at a temperature not exceeding 25°C, protected from direct sunlight.

Keep medicines out of the reach of children

Nature and Contents of Container

BAYLOKIT Combikit (2 + 2 + 2) Capsules & Tablets

Special Precautions for Disposal and Other Handling

No special precaution required for disposal and handling

Marketing Authorization Holder

SIGNATURE PHYTOCHEMICAL INDUSTRIES122, MI,
Selaqui Industrial Area, Dehradun - 248
011. Email: info@signaturepi.in

Marketing Authorization Number(S)

Not applicable

Date of First Authorization/Renewal of the Authorization

Not applicable

Date of Revision of the Text

Not applicable