



CORAL LABORATORIES LTD

ISO 9001:2008 Certificate No. IN015692

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

MODULE 1: ADMINISTRATIVE INFORMATION

PRODUCT: LADACIN [Combipack of 2 Lansoprazole Delayed Release Capsules USP + 2 Tinidazole Tablets + 2 Clarithromycin Tablets USP]

COUNTRY: NIGERIA





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1.1 (Invented) name of the medicinal product :
LADACIN [Combipack of 2 Lansoprazole Delayed Release Capsules USP + 2
Tinidazole Tablets + 2 Clarithromycin Tablets USP]

1.2 Strength :
Lansoprazole USP: 30 mg
(enteric coated pellets)
Tinidazole BP: 500 mg
Clarithromycin USP: 500 mg

1.3 Pharmaceutical form:
Hard Gelatin Capsule & Film coated tablets

2. Qualitative and quantitative composition

Each kit contains:

A. Two Lansoprazole Delayed Release Capsules USP

Each hard gelatin capsule contains:

Lansoprazole USP : 30 mg
(enteric coated pellets)

Excipients : q.s.

Empty gelatin capsule contains approved colours

B. Two Tinidazole Tablets

Each film coated tablet contains:

Tinidazole BP : 500 mg

Excipients : q.s.

Colour: Quinoline Yellow & Titanium Dioxide

C. Two Clarithromycin Tablets USP

Each film coated tablet contains:

Clarithromycin USP : 500 mg

Excipients : q.s.

Colour: Sunset Yellow FCF

Qualitative declaration:

Lansoprazole USP,
Tinidazole BP
Clarithromycin USP

Quantitative declaration:

Lansoprazole USP : 30 mg
(Enteric coated Pellets)
Tinidazole BP : 500 mg
Clarithromycin USP : 500 mg

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3. Pharmaceutical form
Hard Gelatin Capsule & Film coated tablets

4. Clinical particulars:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration

One LADACIN pack contains two capsules of Lansoprazole (30 mg), two tablets of Tinidazole (500 mg) and two tablets of Clarithromycin (500 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.

- **Recommended route of administration** : oral use

4.3 Contraindications

Hypersensitivity to Lansoprazole or Tinidazole or Clarithromycin.

Lansoprazole should not be administered with atazanavir.

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.

Concomitant Administration of Clarithromycin and Any of the Following Drugs is contraindicated

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:

Lansoprazole:

In common with other anti-ulcer therapies, the possibility of malignant gastric tumour should be excluded when treating a gastric ulcer with lansoprazole because lansoprazole can mask the symptoms and delay the diagnosis.

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Lansoprazole should be used with caution in patients with moderate and severe hepatic dysfunction (see sections 4.2 and 5.2).

Decreased gastric acidity due to lansoprazole might be expected to increase gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with lansoprazole may lead to a slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

In patients suffering from gastro-duodenal ulcers, the possibility of H.pylori infection as an etiological factor should be considered.

If lansoprazole is used in combination with antibiotics for eradication therapy of H.pylori, then the instructions for the use of these antibiotics should also be followed.

Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and a thorough risk/benefit assessment should be regularly performed in these patients.

Very rarely cases of colitis have been reported in patients taking lansoprazole. Therefore, in the case of severe and/or persistent diarrhoea, discontinuation of therapy should be considered.

The treatment for the prevention of peptic ulceration of patients in need of continuous NSAID treatment should be restricted to high risk patients (e.g. previous gastrointestinal bleeding, perforation or ulcer, advanced age, concomitant use of medication known to increase the likelihood of upper GI adverse events [e.g. corticosteroids or anticoagulants], the presence of a serious co-morbidity factor or the prolonged use of NSAID maximum recommended doses).

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 lansoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole 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.

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

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Tinidazole

As with related compounds, alcoholic beverages should be avoided during tinidazole therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing tinidazole tablet.

Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with tinidazole abnormal neurological signs develop, therapy should be discontinued.

Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although carcinogenicity data is not available for tinidazole, the two drugs are structurally related and therefore there is a potential for similar biologic effects. Mutagenicity results with tinidazole were mixed (positive and negative) (see section 5.3). The use of tinidazole for longer treatment than usually required should be carefully considered.

Clarithromycin

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2).

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Cases of fatal hepatic failure (see section 4.8) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore,

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discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam (see section 4.5).

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesemia, bradycardia (<50 bpm), or when co-administered with other medicinal products associated with QT prolongation (see section 4.5). Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Pneumonia: In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where *beta*-lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

HMG-CoA Reductase Inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see 4.5).

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Oral hypoglycemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended (see 4.5).

Oral anticoagulants: There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori infection* may select for drug-resistant organisms.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

4.5 Interaction 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

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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.

Theophylline

A minor increase (10%) in the clearance of theophylline was observed following the administration of lansoprazole concomitantly with theophylline. Although the magnitude of the effect on theophylline clearance is small, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Clopidogrel

Concomitant administration of lansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of lansoprazole.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high doses; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted.

In a study of rheumatoid arthritis patients receiving low-dose methotrexate, lansoprazole and naproxen, no effect on pharmacokinetics of methotrexate was observed.

Renal Impairment No dosage adjustment of lansoprazole is necessary in patients with renal impairment. The pharmacokinetics of lansoprazole in patients with various degrees of renal impairment was not substantially different compared with those in subjects with normal renal function.

Hepatic Impairment

In patients with various degrees of chronic hepatic impairment, an increase in the mean AUC of up to 500% was observed at the steady state, compared with healthy subjects. Consider dose reduction in patients with severe hepatic impairment.

Pediatric Use

The safety and effectiveness of lansoprazole has been established in pediatric patients, 1 to 17 years of age, for the short-term treatment of symptomatic gastroesophageal reflux disease (GERD) and erosive esophagitis; however, lansoprazole was not effective in patients with

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symptomatic GERD, 1 month to less than 1 year of age, in a multicenter, double-blind, placebo controlled study.

Geriatric Use

No dosage adjustment of lansoprazole is necessary in geriatric patients. The incidence rates of lansoprazole-associated adverse reactions and laboratory test abnormalities are similar to those seen in younger patients.

Gender

Over 4,000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse reactions in females were similar to those seen in males.

Race

The pooled mean pharmacokinetic parameters of lansoprazole from twelve US Phase 1 studies (N=513) were compared with the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled US data; however, the inter-individual variability was high. The C_{max} values were comparable

Tinidazole

Although not specifically identified in studies with tinidazole, the following drug interactions were reported for metronidazole, a chemically-related nitroimidazole. Therefore, these drug interactions may occur with tinidazole:

Potential Effects of Tinidazole on Other Drugs

Warfarin and other oral coumarin anticoagulants: As with metronidazole, tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation.

Alcohols, Disulfiram

Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during Tinidazole therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram concurrently. Though no similar reactions have been reported with Tinidazole, Tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

Lithium

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Metronidazole has been reported to elevate serum lithium levels. It is not known if Tinidazole shares this property with metronidazole, but consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and Tinidazole treatment to detect potential lithium intoxication.

Phenytoin, fosphenytoin

Concomitant administration of oral metronidazole and intravenous phenytoin was reported to result in prolongation of the half-life and reduction in the clearance of phenytoin. Metronidazole did not significantly affect the pharmacokinetics of orally-administered phenytoin.

Cyclosporine, tacrolimus

There are several case reports suggesting that metronidazole has the potential to increase the levels of cyclosporine and tacrolimus. During Tinidazole co-administration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities.

Fluorouracil

Metronidazole was shown to decrease the clearance of fluorouracil, resulting in an increase in side effects without an increase in therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities.

Potential Effects of Other Drugs on Tinidazole**CYP3A4 inducers and inhibitors**

Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes, i.e. CYP3A4 inducers such as phenobarbital, rifampin, phenytoin and fosphenytoin (a pro-drug of phenytoin), may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Simultaneous administration of drugs that inhibit the activity of liver microsomal enzymes, i.e. CYP3A4 inhibitors such as cimetidine and ketoconazole, may prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma concentrations of tinidazole.

Cholestyramine

Cholestyramine was shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate the dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole.

Oxytetracycline

Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole.

Clarithromycin:

Life-threatening and fatal drug interactions have been reported in patients treated with clarithromycin and colchicine. Clarithromycin is a strong CYP3A4 inhibitor and this interaction

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may occur while using both drugs at their recommended doses. If co-administration of clarithromycin and colchicine is necessary in patients with normal renal and hepatic function, the dose of colchicine should be reduced. Patients should be monitored for clinical symptoms of colchicine toxicity. Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of the C_{max}, C_{min} and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class. Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were co-administered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-OH-clarithromycin were not significantly affected by co-administration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated.

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC₀₋₂₄, and T_{1/2} increases of 30%, 89% and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

Co-administration of clarithromycin with ranitidine bismuth citrate resulted in increased plasma ranitidine concentrations (57%), increased plasma bismuth trough concentrations (48%), and increased 14-OH-clarithromycin plasma concentrations (31%). These effects are clinically insignificant.

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Following

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administration of clarithromycin 500 mg tablets twice daily with zidovudine 100 mg every 4 hours, the steady-state zidovudine AUC decreased 12% compared with administration of zidovudine alone (N=4). Individual values ranged from a decrease of 34% to an increase of 14%. When clarithromycin tablets were administered 2 to 4 hours prior to zidovudine, the steady-state zidovudine C_{max} increased 100%, whereas the AUC was unaffected (N=24). Administration of clarithromycin and zidovudine should be separated by at least 2 hours. The impact of co-administration of clarithromycin extended-release tablets and zidovudine has not been evaluated.

Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Following administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers, the steady-state clarithromycin C_{min} and AUC increased 33% and 18%, respectively. Steady-state concentrations of 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No dosage adjustment of clarithromycin is necessary when co-administered with fluconazole.

Ritonavir

Concomitant administration of clarithromycin and ritonavir (n=22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH-clarithromycin.

Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. Since concentrations of 14-OH-clarithromycin are significantly reduced when clarithromycin is co-administered with ritonavir, alternative antibacterial therapy should be considered for indications other than infections due to *Mycobacterium avium* complex. Doses of clarithromycin greater than 1,000 mg per day should not be co-administered with protease inhibitors.

Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Digoxin

Digoxin is a substrate for P-glycoprotein (P-gp) and clarithromycin is known to inhibit P-gp. When clarithromycin and digoxin are co-administered, inhibition of P-gp by clarithromycin may lead to increased exposure of digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Monitoring of serum digoxin concentrations should be considered, especially for patients with digoxin concentrations in the upper therapeutic range.

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CYP3A

Co-administration of clarithromycin is known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug.

Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following are examples of some clinically significant CYP3A-based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible.

Carbamazepine and Terfenadine

Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-gp. Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When a single dose of colchicine 0.6 mg was administered with clarithromycin 250 mg b.i.d. for 7 days, the colchicine C_{max} increased 197% and the AUC_{0-infinity} increased 239% compared with administration of colchicine alone. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function. Concomitant use of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Oral Hypoglycemic Agents/Insulin

The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of the CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

Efavirenz, Nevirapine, Rifampicin, Rifabutin and Rifapentine

Inducers of CYP3A enzymes, such as efavirenz, nevirapine, rifampicin, rifabutin and rifapentine will increase the metabolism of clarithromycin, thus decreasing plasma concentrations of clarithromycin, while increasing those of 14-OH-clarithromycin. Since the

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microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers. Alternative antibacterial treatment should be considered when treating patients receiving inducers of CYP3A.

Sildenafil, Tadalafil and Vardenafil

Each of these phosphodiesterase inhibitors is primarily metabolized by CYP3A, and CYP3A will be inhibited by concomitant administration of clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil will result in increased exposure of these phosphodiesterase inhibitors. Co-administration of these phosphodiesterase inhibitors with clarithromycin is not recommended.

Tolterodine

The primary route of metabolism for tolterodine is via CYP2D6. However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. Tolterodine 1 mg twice daily is recommended in patients deficient in CYP2D6 activity (poor metabolizers) when co-administered with clarithromycin.

Triazolobenzodiazepines (e.g. Alprazolam, Midazolam, Triazolam)

When a single dose of midazolam was co-administered with clarithromycin tablets (500 mg twice daily for 7 days), midazolam AUC increased 174% after intravenous administration of midazolam and 600% after oral administration. When oral midazolam is co-administered with clarithromycin, dose adjustments may be necessary and possible prolongation and intensity of effect should be anticipated. Caution and appropriate dose adjustments should be considered when triazolam or alprazolam is co-administered with clarithromycin. For benzodiazepines which are not metabolized by CYP3A (e.g. temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been postmarketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Following administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily), the clarithromycin AUC increased 94%, the 14-OH-clarithromycin AUC decreased 70%, and the atazanavir AUC increased 28%. When clarithromycin is co-administered with atazanavir, the dose of clarithromycin should be decreased by 50%. Since concentrations of 14-OH-clarithromycin are significantly reduced when clarithromycin is co-administered with atazanavir, alternative antibacterial therapy should

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be considered for indications other than infections due to *Mycobacterium avium* complex. Doses of clarithromycin greater than 1,000 mg per day should not be co-administered with protease inhibitors.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when administered concomitantly. Clarithromycin may increase the plasma concentrations of itraconazole, while itraconazole may increase the plasma concentrations of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and there is evidence of a bi-directional drug interaction. Following administration of clarithromycin (500 mg b.i.d.) and saquinavir (soft gelatin capsules, 1,200 mg t.i.d.) to 12 healthy volunteers, the steady-state saquinavir AUC and C_{max} increased 177% and 187%, respectively, compared with administration of saquinavir alone. Clarithromycin AUC and C_{max} increased 45% and 39%, respectively, whereas the 14-OH-clarithromycin AUC and C_{max} decreased 24% and 34%, respectively, compared with administration with clarithromycin alone. No dose adjustment of clarithromycin is necessary when clarithromycin is co-administered with saquinavir in patients with normal renal function. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

The following CYP3A-based drug interactions have been observed with erythromycin products and/or with clarithromycin in postmarketing experience:

Anti-arrhythmics

There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum concentrations of these medications should also be monitored.

Ergotamine/dihydroergotamine

Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues, including the CNS. Concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated.

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Triazolobenzodiazepines (such as Triazolam and Alprazolam) and related Benzodiazepines (such as Midazolam)

Erythromycin has been reported to decrease the clearance of triazolam and midazolam and, thus, may increase the pharmacologic effect of these benzodiazepines. There have been postmarketing reports of drug interactions and CNS effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

Sildenafil

Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin; reduction of sildenafil dosage should be considered.

There have been spontaneous or published reports of CYP3A-based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, bromocriptine and vinblastine.

Concomitant administration of clarithromycin with cisapride, pimozone, astemizole or terfenadine is contraindicated.

In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin and valproate.

Oral Anticoagulants

There is a risk of serious hemorrhage and significant elevations in the INR and prothrombin time when clarithromycin is co-administered with warfarin. The INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

HMG-CoA Reductase Inhibitors

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy.

Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin or pravastatin) should be considered.

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4.6 Pregnancy and lactation

Lansoprazole, Tinidazole, Clarithromycin:

There are not well controlled studies of lansoprazole or Tinidazole or Clarithromycin in pregnant women. Hence this Combikit is not indicated in pregnancy.

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 **LADACIN** 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:

Not Stated.

4.8 Undesirable effects:

Lansoprazole

Clinical Trial Experience

Worldwide, over 10,000 patients have been treated with Lansoprazole in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. In general, Lansoprazole treatment has been well tolerated in both short-term and long-term trials. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The following adverse reactions were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of Lansoprazole-treated patients and occurred at a greater rate in Lansoprazole-treated patients than placebo-treated patients in the table below:

Table 3: Incidence of Possibly or Probably Treatment-Related Adverse Reactions in Short-Term, Placebo-Controlled Lansoprazole Studies

Body System/Adverse	Lansoprazole	Placebo
Event	(N= 2,768) %	(N=1,023) %

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<i>Body as a Whole</i>		
Abdominal pain	2.1	1.
<i>Digestive System</i>		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo.

The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of Lansoprazole, but higher in the patients who received 60 mg of Lansoprazole (2.9%, 1.4%, 4.2% and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of Lansoprazole for non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers, the incidence of diarrhea for patients treated with Lansoprazole, misoprostol, and placebo was 5%, 22% and 3%, respectively.

Another study for the same indication, where patients took either a COX-2 inhibitor or Lansoprazole and naproxen, demonstrated that the safety profile was similar to the prior study. Additional reactions from this study, not previously observed in other clinical trials with Lansoprazole included contusion, duodenitis, epigastric discomfort, esophageal disorder, fatigue, hunger, hiatal hernia, hoarseness, impaired gastric emptying, metaplasia, and renal impairment.

Additional adverse experiences occurring in less than 1% of patients or subjects who received Lansoprazole in domestic trials are shown below:

Body as a Whole

Abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest

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pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain.

Cardiovascular System

Angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation.

Digestive System

Abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, gastrointestinal moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis.

Endocrine System

Diabetes mellitus, goiter, hypothyroidism.

Hemic and Lymphatic System

Anemia, hemolysis, lymphadenopathy.

Metabolism and Nutritional Disorders

Avitaminosis, gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss.

Musculoskeletal System

Arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, ptosis, synovitis.

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Nervous System

Abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, dementia, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo.

Respiratory System

Asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, lung fibrosis, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, and stridor.

Skin and Appendages

Acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria.

Special Senses

Abnormal vision, amblyopia, blepharitis, blurred vision, cataract, conjunctivitis, deafness, dry eyes, ear/eye disorder, eye pain, glaucoma, otitis media, parosmia, photophobia, retinal degeneration/disorder, taste loss, taste perversion, tinnitus, visual field defect.

Urogenital System

Abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary retention, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing Experience

Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these reactions were reported voluntarily from a population of

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unknown size, estimates of frequency cannot be made. These events are listed below by the COSTART body system.

Body as a Whole: Anaphylactic/anaphylactoid reactions.

Digestive System: Hepatotoxicity, pancreatitis, vomiting.

Hemic and Lymphatic System: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura.

Metabolism and Nutritional Disorders: Hypomagnesemia.

Musculoskeletal System: Bone fracture, myositis.

Skin and Appendages: Severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

Special Senses: Speech disorder.

Urogenital System: Interstitial nephritis, urinary retention.

Laboratory Values

The following changes in laboratory parameters in patients who received lansoprazole were reported as adverse reactions:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal white blood cells (WBCs), abnormal AG ratio, abnormal red blood cells (RBCs), bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased, hyperlipaemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo-controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2,677) patients, who received placebo and lansoprazole, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received lansoprazole reported jaundice at any time during the study.

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In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

Tinidazole

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Among 3,669 patients treated with a single 2 g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and giardiasis clinical studies, adverse reactions were reported by 11.0% of patients. For multi-day dosing in controlled and uncontrolled amebiasis studies, adverse reactions were reported by 13.8% of 1,765 patients. Common ($\geq 1\%$ incidence) adverse reactions reported by body system are as follows. (Note: Data described in the table below are pooled from studies with variable designs and safety evaluations.)

Other adverse reactions reported with tinidazole included the following:

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.

Blood and Lymphatic System Disorders: Leukopenia.

Skin and Subcutaneous Tissue Disorders: Dermatitis allergic, pruritus, urticaria, and angioedema.

Immune System Disorders: Drug hypersensitivity.

Renal and Urinary Disorders: Chromaturia.

Cardiovascular: Palpitations.

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Other: Candida overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities, including raised transaminase level, arthralgias, myalgias, and arthritis.

Table 4: Adverse Reactions Summary of Published Reports

	2 g Single Dose	Multi-day Dose
Gastrointestinal		
Metallic/bitter taste	3.7%	6.3%
Nausea	3.2%	4.5%
Anorexia	1.5%	2.5%
Dyspepsia/cramps/epi-gastric discomfort	1.8%	1.4%
Vomiting	1.5%	0.9%
Constipation	0.4%	1.4%
CNS		
Weakness/fatigue/malaise	2.1%	1.1%
Dizziness	1.1%	0.5%
Other		
Headache	1.3%	0.7%
Total patients with adverse reactions	11.0% (403/3,669)	13.8% (244/1,765)

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Rare reported adverse reactions include bronchospasm, dyspnea, coma, confusion, depression, furry tongue, pharyngitis and reversible thrombocytopenia.

Adverse Reactions in Pediatric Patients

In pooled pediatric studies, adverse reactions reported in pediatric patients taking tinidazole were similar in nature and frequency to adult findings, including nausea, vomiting, diarrhea, taste change, anorexia, and abdominal pain.

Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of tinidazole. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Severe acute hypersensitivity reactions have been reported on initial or subsequent exposure to tinidazole. Hypersensitivity reactions may include urticaria, pruritus, angioedema, Stevens-Johnson syndrome and erythema multiforme.

Clarithromycin

Clinical Trial Experience

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. These adverse reactions are consistent with the known safety profile of macrolide antibiotics. There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

The following adverse reactions were observed in clinical trials with clarithromycin at a rate greater than or equal to 1%:

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.

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Psychiatric Disorders: Insomnia.

Skin and Subcutaneous Tissue Disorders: Rash.

The following adverse reactions were observed in clinical trials with clarithromycin at a rate less than 1%:

Blood and Lymphatic System Disorders: Leukopenia, neutropenia, thrombocytopenia, eosinophilia.

Cardiac Disorders: Electrocardiogram QT prolonged, cardiac arrest, atrial fibrillation, extrasystoles, palpitations.

Ear and Labyrinth Disorders: Vertigo, tinnitus, hearing impaired.

Gastrointestinal Disorders: Stomatitis, glossitis, esophagitis, GERD, gastritis, proctalgia, abdominal distension, constipation, dry mouth, eructation, flatulence.

General Disorders and Administration Site Conditions: Malaise, pyrexia, asthenia, chest pain, chills, fatigue.

Hepatobiliary Disorders: Cholestasis, hepatitis.

Immune System Disorders: Hypersensitivity.

Infections and Infestations: Cellulitis, gastroenteritis, infection, vaginal infection.

Investigations: Blood bilirubin increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, albumin globulin ratio abnormal.

Metabolism and Nutrition Disorders: Anorexia, decreased appetite.

Musculoskeletal and Connective Tissue Disorders: Myalgia, muscle spasms, nuchal rigidity.

Nervous System Disorders: Dizziness, tremor, loss of consciousness, dyskinesia, somnolence.

Psychiatric Disorders: Anxiety, nervousness.

Renal and Urinary Disorders: Blood creatinine increased, blood urea increased.

Respiratory, Thoracic and Mediastinal Disorders: Asthma, epistaxis, pulmonary embolism.

Skin and Subcutaneous Tissue Disorders: Urticaria, dermatitis bullous, pruritus, hyperhidrosis, rash maculo-papular.

In community-acquired pneumonia studies conducted in adults comparing clarithromycin with erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared with erythromycin-treated patients (13% vs. 32%; p

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Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of clarithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Blood and Lymphatic System Disorders: Thrombocytopenia, agranulocytosis.

Cardiac Disorders: Torsades de pointes, ventricular tachycardia, ventricular arrhythmia.

Ear and Labyrinth Disorders: Deafness was reported chiefly in elderly women and was usually reversible.

Gastrointestinal Disorders: Pancreatitis acute; tongue discoloration, tooth discoloration was reported and was usually reversible with professional cleaning upon discontinuation of the drug. There have been reports of clarithromycin tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibacterial drug.

Hepatobiliary Disorders: Hepatic failure, jaundice hepatocellular. Adverse reactions related to hepatic dysfunction have been reported with clarithromycin.

Immune System Disorders: Anaphylactic reaction.

Infections and Infestations: Pseudomembranous colitis.

Investigations: Prothrombin time prolonged, WBC count decreased, INR increased. Abnormal urine color has been reported, associated with hepatic failure.

Metabolism and Nutrition Disorders: Hypoglycemia has been reported in patients taking oral hypoglycemic agents or insulin.

Musculoskeletal and Connective Tissue Disorders: Myopathy and rhabdomyolysis were reported and in some of the reports, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol.

Nervous System Disorders: Convulsion, ageusia, parosmia, anosmia, paresthesia.

Psychiatric Disorders: Psychotic disorder, confusional state, depersonalization, depression, disorientation, manic behavior, hallucination, abnormal behavior, abnormal dreams. These disorders usually resolve upon discontinuation of the drug. There are no data on the effect of

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clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

Renal and Urinary Disorders: Nephritis interstitial, renal failure.

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, acne.

Vascular Disorders: Hemorrhage.

There have been reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance were as follows:

Hepatic: Elevated SGPT (ALT) **Hematologic:** Decreased WBC **Renal:** Elevated BUN, 4%; elevated serum creatinine

Note: GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

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 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

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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., *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.

Clarithromycin

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 *Haemophilus 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 *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Moraxella* (*Branhamella*) *catarrhalis*, *Neisseria gonorrhoeae*, *H. pylori* and *Campylobacter* spp.

5.2 Pharmacokinetic Properties

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**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 (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 (\pm SD) plasma half-life was 1.5 (\pm 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**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 (\pm 7.5) mcg/mL, with a mean time to peak concentration (T_{max}) of 1.6 (\pm 0.7) hours, and a mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) of 901.6 (\pm 126.5) mcg.hr/mL at 72 hours. The elimination half-life ($T_{1/2}$)

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was 13.2 (\pm 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 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 $T_{1/2}$ 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 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

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

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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.

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.

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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 Sprague-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.

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6. Pharmaceutical particulars

6.1 List of excipients

Lansoprazole Delayed-Release Capsules

1. Lansoprazole Pellets IH
2. N.P. Seeds IH
3. EHG caps "1" Red / White IH

Tinidazole Tablets

1. Lactose BP
2. Maize Starch BP
3. Povidone K-30 USP
4. Gelatin BP
5. Sodium Methyl Paraben BP
6. Sodium Propyl Paraben BP
7. Purified Water BP
8. Magnesium Stearate BP
9. Colloidal Anhydrous Silica BP
10. Sodium Starch Glycolate BP
11. Hypromellose 15 CPS BP
12. Titanium Dioxide BP
13. Purified Talc BP
14. Macrogol (PEG 400) BP
15. Quinoline Yellow Lake IH
16. Isopropyl Alcohol BP
17. Dichloromethane BP

Clarithromycin Tablets USP

1. Lactose BP
2. Maize Starch BP
3. Colloidal Anhydrous Silica BP
4. Povidone K-30 USP
5. Macrogol 400 BP
6. Isopropyl Alcohol BP
7. Purified Talc BP
8. Hypromellose 15 CPS BP
9. Titanium Dioxide BP
10. Sunset Yellow FCF IH
11. Dichloromethane BP
12. Indion 234 IH

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

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6.4 Special precautions for storage

Store in a cool & dry place. Protect from heat, light & moisture.

Keep medicine out of reach of children.

6.5 Nature and contents of container

LADACIN

(Combipack of 2 Lansoprazole Delayed Release Capsules USP + 2 Tinidazole Tablets + 2 Clarithromycin Tablets USP) is a special combikit of 4 Tablets and 2 capsules packed in Alu-PVC Blister pack. Such 7 kits to be packed in a carton along with pack insert. Such 2 cartons to be packed in outer carton.

Each kit contains:

2 Lansoprazole Gastro resistant Capsules BP 30 mg

2 Tinidazole Tablets 500 mg and

2 Clarithromycin Tablets USP 500 mg.

6.6 Special precautions for disposal:

None

7. Registrant:

MARKETING AUTHORISATION HOLDER

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8. Date of revision of the text: NA

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