SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GASTRO KIT (Lansoprazole, Clarithromycin and Tinidazole Combi kit)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COMPOSITION:

Each Combi kit Contains:

A. Two Lansoprazole Delayed Release Capsules USP 30 mg:

Each Hard Gelatin Capsule Contains:

Lansoprazole USP…...30 mg

(As enteric coated pellets)

Excipients ……q.s

Approved Colour is used in empty capsule shells

B. Two Clarithromycin Tablets USP 250 mg
Each Film Coated Tablets Contains
Clarithromycin USP…250 mg
Excipients …….q.s
Colour: Titanium Dioxide

C. Two Tinidazole Tablets 500 mg
Each Film-Coated Tablet Contains:
Tinidazole USP….500 mg
Excipients ……q.s
Colour: Sunset Yellow

Excipients
Sugar
As lansoprazole contains sugar, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. 7% Sugar concentration is used in the formulation of pellets.

Sodium Methyl Hydroxybenzoate
Sodium Methyl Hydroxybenzoate has no teratogenic, carcinogenic, mutagenic or embryotoxic toxicity in the amounts at which it is used as 0.1%.

Sodium Propyl Hydroxybenzoate
Sodium Propyl Hydroxybenzoate has no teratogenic, carcinogenic, mutagenic or embryotoxic toxicity in the amounts at which it is used as 0.1%.

Sunset Yellow:
The acceptable daily intake (ADI) is 0–4 mg/kg under both EU and WHO/FAO guidelines. Sunset Yellow FCF has no carcinogenicity, genotoxicity, or developmental toxicity in the amounts at which it is used.

3. PHARMACEUTICAL FORM

A. Lansoprazole Delayed Release Capsules USP 30 mg
Hard Gelatin Capsule
Pink / Clear transparent size '2' hard gelatin capsules containing white to off white colour pellets.

B. Clarithromycin Tablets USP 250 mg
Film coated tablets
White Colour, round shaped coated tablets plain on both side.

C. Tinidazole Tablets 500 mg
Film coated tablets
Orange color, Capsule shaped, film coated tablet with break line on one side and plain on other side.
The score line is not intended for division of the tablet. The tablet should be swallowed whole.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GASTRO KIT is used for Vaginal or stomach infections, Acidic stomach, Lungs infection, Community acquired pneumonia, Stomach ulcers and NSAID induced ulcers.

4.2 Posology and method of administration

Route of administration: Oral
The Kit is not recommended for children younger than 12 years.
Adults: GASTRO KIT as single oral dose, or as prescribed.
One GASTRO KIT pack contains two capsules of Lansoprazole (30 mg), two tablets of Tinidazole (500 mg) and two tablets of Clarithromycin (250 mg).

One pack is for 1 day of treatment. From this specially designed pack, one capsule of Lansoprazole, one tablet of Tinidazole and one tablet of Clarithromycin is to be taken in the morning and similarly one each in the evening. The duration of therapy recommended is for 7 days.

4.3 Contraindications

Lansoprazole

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clarithromycin

Clarithromycine is contraindicated in patients with hypersensitivity to clarithromycin, to other macrolides or azalide antibacterial agents, or to any of the excipients listed in section 6.1. - Concomitant administration with ticagrelor or ranolazine is contraindicated. - Patients taking ergot derivatives. Concomitant administration of clarithromycin and ergotamine or

dihydroergotamine is contraindicated, as this may result in ergot toxicity. - Concomitant administration of clarithromycin with oral midazolam is contraindicated (see section 4.5). - Patients taking any of astemizole, cisapride, domperidone, pimozide or terfenadine. Elevated plasma levels of cisapride, pimozide and terfenadine have been measured in patients receiving concomitant clarithromycin. This may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides (see sections 4.4 and 4.5). - Patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see sections 4.4 and 4.5) - Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.4). Page 4 of 41 - Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT-interval) - Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment. - As with other strong CYP3A4 inhibitors, clarithromycin should not be used in patients taking colchicine. - Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5)

Tinidazole

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

As with other drugs of similar structure, tinidazole is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal studies.

Tinidazole should be avoided in patients with organic neurological disorders.

Tinidazole, other 5-nitroimidazole derivatives or any of the components of this product should not be administered to patients with known hypersensitivity to the drug.

Use of tinidazole is contraindicated during the first trimester of pregnancy and in nursing mothers (see section 4.6).

4.4 Special warnings and precautions for use

Lansoprazole

Gastric Malignancy

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy

Clostridium difficile Associated Diarrhea

Published observational studies suggest that proton pump inhibitor (PPI) therapy like LANSOPRAZOLE may be associated with an increased risk of Clostridium 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. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Lansoprazole.

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-

term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines .

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Concomitant Use of LANSOPRAZOLE with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Excipients

Sugar

As lansoprazole contains sugar, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium Methyl Hydroxybenzoate

Sodium Methyl Hydroxybenzoate has no teratogenic, carcinogenic, mutagenic or embryotoxic toxicity in the amounts at which it is used.

Sodium Propyl Hydroxybenzoate

Sodium Propyl Hydroxybenzoate has no teratogenic, carcinogenic, mutagenic or embryotoxic toxicity in the amounts at which it is used.

Sunset Yellow:

The acceptable daily intake (ADI) is 0–4 mg/kg under both EU and WHO/FAO guidelines. Sunset Yellow FCF has no carcinogenicity, genotoxicity, or developmental toxicity in the amounts at which it is used.

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.

Clarithromycin is mainly metabolised 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.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. 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. Clostridioides difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea 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 diarrhoea 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, 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 colchicine and clarithromycin is contraindicated (see section 4.3).
Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous midazolam (see section 4.5).
As with other antibiotics when renal function is poor, dosage of clarithromycin should be suitably reduced depending on the degree of the impairment (see section 4.2). In elderly patients, the possibility of renal impairment should be considered.
Clarithromycin can be used in patients with known hypersensitivity to penicillin or when penicillin would be inappropriate for other reasons.
Attention should be paid to the possible cross-resistance and cross-allergy between clarithromycin and other macrolides, clindamycin and lincomycin.
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 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 nonsusceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Cardiovascular Events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk of ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients:

- Patients with a coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
- Clarithromycin must not be given to patients with electrolye disturbances such as hypomagnesaemia or hypokalaemia (see section 4.3)
- Patients concomitantly taking other medicinal products associated with a QT prolongation (see section 4.5)

- Concomitant administration of clarithromycin with astemizole, cisapride, domperidone, pimozide and terfenadine is contraindicated (see section 4.3)
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia:
In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for communityacquired pneumonia. In hospital-acquired pneumonia clarithromycin should only be used in combination with further 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 species are often resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases, where beta lactams cannot be used (e.g. allergy towards beta lactams) other antibiotics, such as clindamycin, are the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections such as infections caused by Corynebacterium minutissimum (erythrasma), acne vulgaris, and in erysipelas and in situations where penicillin treatment is not possible.
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.
Clarithromycin should be used with caution when administered concurrently with medicines that induce CYP3A4 due to the possibility of subtherapeutic levels of clarithromycin (see section 4.5). Page 6 of 41 Clarithromycin is an inhibitor of CYP3A4 and concomitant use with other medicinal products that are metabolised to a large extent by this enzyme should be restricted to situations where it is clearly indicated (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 possible dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).
Oral hypoglycaemic agents/insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulfonylureas) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended (see section 4.5).

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalised 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.
Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).

Streptococcus pyogenes: Clarithromycin is generally effective in the eradication of Streptococci from the oropharynx. However, data establishing the efficacy of this antibiotic in the subsequent prevention of rheumatic fever are not available.

In pharyngitis related to beta-haemolytic streptococcal infection the treatment duration should be at least 10 days.

There is a potential for clarithromycin to affect the plasma levels and activity of a range of other medicinal products and vice versa. Clarithromycin must not be co-administered with certain other medicinal products (see section 4.3). In addition, section 4.5 provides details of potential drug interactions and should be followed with care.

This medicine contains less than I mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'**.**

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 .
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.

4.5 Interaction with other medicinal products and other forms of interaction
Lansoprazole
Effects of lansoprazole on other medicinal products
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 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 *[see Clinical Pharmacology (12.3)]*. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in 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 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.

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 dose; 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.

Combination Therapy with Clarithromycin

Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [see Warnings and Precautions in prescribing information for clarithromycin]. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs [see Contraindications in prescribing information for clarithromycin].

For information about drug interactions of antibacterial agents (amoxicillin and clarithromycin) indicated in combination with LANSOPRAZOLE, refer to the DRUG INTERACTIONS section of their package inserts.

Clarithromycin

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Asternizole, cisapride, domperidone, pimozide and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pirnozide concomitantly (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two- to three-fold increase in the serum level of the acid metabolite ofterfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine

Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

Lomitapide

Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases (see section 4.3).

<u>Oral Midazolam</u>

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated (see section 4.3).

<u>HMG-CoA reductase inhibitors (statins)</u>

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3) as these statins are extensively metabolised by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking

clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or
simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. 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. Patients should be monitored for signs and symptoms of myopathy.

The effect of other medicinal products on clarithromycin tablets

Drugs that are inducers ofCYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin;
clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-0H-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-0H clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers. A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-hydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

In such circumstances, it may be necessary to increase the dose of clarithromycin and monitor the safety and efficacy. Monitoring the plasma levels of the CYP3A4 inducer may be necessary because

the levels could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant medicinal product information for the CYP3A4 inducer administered).

Etravirine
Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-0H-clarithromycin, were increased. Because 14-0H-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen

may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to
21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cutin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-0H-clarithromycin were not significantly affected by concomitant administration offluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-0H-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLcR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be coadministered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional drug interactions).

The effect of clarithromycin tablets on other medicinal products

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A, may be associated with elevations in drug concentrations that could increase or prolong both 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 metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin. Alternatively, treatment with these medicinal products may be interrupted during clarithromycin treatment.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, domperidone, ergot alkaloids, ibrutinib, lomitapide lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

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

There have been post marketing reports ofhypoglycaemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Direct acting oral anticoagulants (DOACs)

The DOAC dabigatran is a substrate for the effiux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Oral hypoglycaemic agents/insulin

With certain hypoglycaemic drugs such as nateglinide and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole

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}, AUC_{0-24}, and $t_{1/2}$ increased by 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 omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil, and vardenafil

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and

vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant (p<:::0.05) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid ofCYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition ofCYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser population.

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after *intravenous administration* of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If *intravenous midazolam* is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely. There have been post-marketing 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.

There are not any *in vivo* human data describing interactions between clarithromycin and the following medicinal products: prepatent, halofantrine and ziprasidone. However, as the *in vitro* data appear to indicate that the medicinal products are substrates of CYP3A, their concomitant administration with clarithromycin should be carried out with caution.

Concomitant administration of eletriptan with CYP3A inhibitors, such as clarithromycin, is contraindicated.

Ciclosporin, tacrolimus and sirolimus

Concomitant use of oral clarithromycin has resulted in more than a 2-fold increase of the Cmin-levels of both ciclosporin and tacrolimus. Similar effects are also expected for

sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, ciclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses decreased as necessary. When clarithromycin is discontinued, plasma levels should guide the re-adjustment of doses of ciclosporin, tacrolimus or sirolimus.

Clarithromycin antagonises the bactericidal effect of beta-lactam antibiotics. Warfarin

Clarithromycin may potentiate the effects of warfarin. The prothrombin time should be monitored frequently and doses of warfarin adjusted as necessary.

Rifabutin

Concomitant administration of rifabutin and clarithromycin resulted in an increase and decrease, respectively, in plasma levels. An increased risk of uveitis associated with rifabutin may occur.

Fluconazole

Clarithromycin may increase plasma concentrations of fluconazole.

Other drug interactions

Aminoglycosides

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides (see section 4.4)

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Concomitant administration of clarithromycin and colchicine is contraindicated (see sections 4.3 and 4.4).

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously

administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxy inosine. This interaction is unlikely when clarithromycin is administered via *intravenous* infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised by CYP3A (e.g., phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported

Bi-directional drug interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-0H-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance
30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine
clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co administered with protease inhibitors.

Calcium channel blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolised by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saguinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in
steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

Tinidazole

Alcohol: Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided.

Anticoagulants: Drugs of similar chemical structure have been shown to potentiate the effects of oral anticoagulants. Prothrombin time should be closely monitored and adjustments to the dose of the anticoagulants should be made as necessary.

4.6 Fertility, pregnancy and lactation

Lansoprazole, Tinidazole, Clarithromycin

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

Lactation

Lansoprazole, Tinidazole, Clarithromycin

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

Woman should not nurse until at least 3days after having discontinued taking Tinidazole.

Pediatric Use

Safety and effectiveness of GASTRO KIT in the pediatric population have not been established.

Renal and Hepatic Impairment

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

4.7 Effects on ability to drive and use machines

There are no data on the effect of GASTRO KIT 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.

4.8 Undesirable effects
Lansoprazole

Low magnesium levels in your body. This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.

- seizures
- dizziness
- abnormal or fast heartbeat
- jitteriness
- jerking movements or shaking (tremors)
- muscle weakness
- spasms of the hands and feet
- cramps or muscle aches
- spasm of the voice box

The most common side effects of LANSOPRAZOLE in adults and children include:

- diarrhea
- stomach pain
- nausea
- constipation
- headache

Other side effects:

Serious allergic reactions. Tell your doctor if you get any of the following symptoms with LANSOPRAZOLE.

- rash
- face swelling
- throat tightness
- difficulty breathing

Clarithromycin
a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics (see section b of section 4.8).

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	Very common (≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known (cannot be estimated from the available data)
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			Anaphylactoid reaction[1], Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[6], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing, impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged[7], extrasystoles[1], palpitations	Torsade de pointes[7], ventricular tachycardia[7] ventricular fibrillation
Vascular disorders		Vasodilation[1]		Hemorrhage[8]
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	

Gastrointestinal disorders		Diarrhea[9], vomiting, dyspepsia, nausea, abdominal pain	Esophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased4	Hepatic failure[10], jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome[5], toxic epidermal necrolysis[5], drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2, 11], myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1] , blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased[8], prothrombin time prolonged[8], urine color abnormal

1 ADRs reported only for the Powder for Solution for Injection formulation
2ADRs reported only for the Extended-Release Tablets formulation
3 ADRs reported only for the Granules for Oral Suspension formulation
4 ADRs reported only for the Immediate-Release Tablets formulation
5, 7, 9, 10, See section a)
6, 8, 11 See section c)

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.
In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome (see sections 4.4 and 4.5).

There have been post-marketing 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 (see section 4.5).

There have been rare reports of clarithromycin ER 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 antibiotic.
Special population: Adverse Reactions in Immunocompromised Patients (see section e)

d. Paediatric populations
Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.
e. Other special populations
Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.
In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1,000 mg and 2,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1,000 mg and 2,000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4,000 mg of clarithromycin.
In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who

received 1,000 mg or 2,000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4,000 mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Tinidazole
Reported side effects have generally been infrequent, mild and self-limiting.

The reported undesirable effects are listed below according to MedDRA system organ class classification and frequency. Within each frequency category, the ADRs are presented in the order of clinical importance. Frequency categories are expressed as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (the frequency cannot be estimated from the available data).

System Organ Class	*Common*	*Not known*
Blood and the lymphatic system disorders		Leukopenia
Immune system disorders		Drug hypersensitivity
Metabolism and nutrition disorders	Decreased appetite	
Nervous system disorders	Headache	Convulsions Neuropathy peripheral Paraesthesia Hypoaesthesia Sensory disturbances Ataxia Dizziness Dysgeusia
Ear and labyrinth disorders	Vertigo	
Vascular disorders		Flushing
Gastrointestinal disorders	Vomiting Diarrhoea Nausea Abdominal pain	Glossitis Stomatitus Tongue discolouration
Skin and subcutaneous tissue disorders	Dermatitis allergic Pruritis	Angioedema Urticaria
Renal and urinary disorders		Chromaturia
General disorders and administration site conditions		Pyrexia Fatigue

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

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

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC03

Lansoprazole is a gastric proton pump inhibitor. 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 sulphydryl group of H+/K+ATPase causing inhibition of the enzyme activity.

Effect on gastric acid secretion

Lansoprazole is a specific inhibitor of the parietal cell proton pump. A single oral 30 mg dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by about 80%. After repeated daily administration for seven 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 very first dose. After eight 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, patients with gastric ulcer and reflux oesophagitis within 4 weeks. By reducing gastric acidity, lansoprazole creates an environment in which appropriate antibiotics can be effective against H. pylori.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. AlsoCgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Clarithromycin
Pharmacotherapeutic group: Macrolides

ATC code: J01FA09
Mode of action:
Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.
The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or twofold higher than the MICs of the parent compound, except for H. influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.

PK/PD relationship
Clarithromycin is extensively distributed into body tissues and fluids. Due to the high tissue penetration, intracellular concentrations higher than serum concentrations. The main

pharmacodynamic parameters to predict macrolide activities are unconvincing established. The time above the MIC (T / MIC) is the best determinant for the efficacy of clarithromycin. Because the concentrations of clarithromycin in the lung tissues and epithelial tissue fluid reaches the plasma concentrations exceed, the use of plasma concentrations-based parameters are insufficient to accurately predict response for respiratory infections.

Mechanisms of resistance:
Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exist constitutively.

Macrolide resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramine B based on methylation of the ribosomal binding site. Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes. A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant Streptococcus pneumoniae are resistant to macrolides such as clarithromycin.

Tinidazole
Pharmacotherapeutic group: Antiinfectives for systemic use

ATC code: J 01XD02

TINIDAZOLE is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia.

The mode of action of TINIDAZOLE against anaerobic bacteria and protozoa involves penetration of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.

TINIDAZOLE is active against Helicobacter 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.

Helicobacter pylori (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 omeprazole and clarithromycin eradicates 91-96% of H.pylori isolates.

Various different H.pylori eradication regimens have shown that eradication of H.pylori heals duodenal ulcers and reduces the risk of ulcer recurrence.

5.2 Pharmacokinetic properties

Lansoprazole

Lansoprazole is a racemate of two active enantiomers that are bio transformed into the active form in the acidic environment of the parietal cells. As lansoprazole is rapidly inactivated by gastric acid, it is administered orally in enteric-coated form(s) for systemic absorption.

Absorption and distribution

Lansoprazole exhibits high (80-90%) bioavailability with a single dose. Peak plasma levels occur within 1.5 to 2.0 hours. Intake of food slows the absorption rate of lansoprazole and reduces the bioavailability by about 50%. The plasma protein binding is 97%.

Studies have shown that granules from opened capsules give equivalent AUC as the intact capsule if the granules are suspended in a small amount of orange juice, apple juice, or tomato juice mixed with a tablespoon of apple or pear puree or sprinkled on a tablespoon of yoghurt, pudding or cottage cheese. Equivalent AUC has also been shown for granules suspended in apple juice administered through a naso-gastric tube.

Biotransformation and elimination

Lansoprazole is extensively metabolised by the liver and the metabolites are excreted by both the renal and biliary route. The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19. The enzyme CYP3A4 also contributes to the metabolism. The plasma elimination half-life ranges from 1 to 2 hours following single or multiple doses in healthy subjects. There is no evidence of accumulation following multiple doses in healthy subjects. Sulphone, sulphide and 5-hydroxyl derivatives of lansoprazole have been identified in plasma. These metabolites have very little or no antisecretory activity.

A study with 14C labelled lansoprazole indicated that approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces.

Pharmacokinetics in elderly patients

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Peak plasma levels were not increased in the elderly.

Pharmacokinetics in paediatric patients

The evaluation of the pharmacokinetics in children aged 1 –17 years of age showed a similar exposure as compared to adults with doses of 15 mg for those below 30 kg of weight and 30 mg for those above.

The investigation of a dose of 17 mg/m2 body surface or 1 mg/kg body weight also resulted in comparable exposure of lansoprazole in children aged 2-3 months up to one year of age compared to adults.

Higher exposure to lansoprazole in comparison to adults has been seen in infants below the age of 2-3 months with doses of both 1.0 mg/kg and 0.5 mg/kg body weight given as a single dose.

Pharmacokinetics in hepatic insufficiency
The exposure of lansoprazole is doubled in patients with mild hepatic impairment and much more increased in patients with moderate and severe hepatic impairment.

CYP2C19 poor metabolisers

CYP2C19 is subject to genetic polymorphism and 2-6 % of the population, called poor metabolisers (PMs), are homozygote for a mutant CYP2C19 allele and therefore lacks a functional CYP2C19 enzyme. The exposure of lansoprazole is several-fold higher in PMs than in extensive metabolisers (EMs).

Clarithromycin

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum – but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml. After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:
Clarithromycin penetrates well into different compartments with an estimated volume of distribution of 200-400 l. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating drug levels. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism is in the liver involving the P450 cytochrome system. Three metabolites are described: N-demethyl clarithromycin, decladinosyl clarithromycin and 14-hydroxy clarithromycin. The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. Elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.

Approximately 20 -40% of clarithromycin is excreted as the unchanged active substance in the urine. This proportion is increased when the dose is increased. An additional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest is excreted in the faeces.Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased. Total plasma clearance has been estimated to approximately 700 mL/min (11,7 mL/s), with a renal clearance of approximately 170 mL/min (2,8 mL/s).

Special populations:
Renal impairment: Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

Tinidazole

TINIDAZOLE is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2g tinidazole orally, peak serum levels of 40-51 micrograms/ml were achieved within two hours and decreased to between 11-19 micrograms/ml at 24 hours. Healthy volunteers who received 800mg and 1.6g tinidazole IV over 10-15 minutes achieved peak plasma concentrations that ranged from 14 to 21mcg/ml for the 800mg dose and averaged 32mcg/ml for the 1.6g dose. At 24 hours post infusion, plasma levels of tinidazole decreased to 4-5mcg/ml and 8.6mcg/ml respectively, justifying once daily dosing. Plasma levels decline slowly and tinidazole can be detected in plasma at concentrations of up to 1 microgram/ml at 72 hours after oral administration. The plasma elimination half-life for tinidazole is between 12-14 hours.

Tinidazole is widely distributed in all body tissues and also crosses the blood brain barrier, obtaining clinically effective concentrations in all tissues. The apparent volume of distribution is about 50 litres. About 12% of plasma tinidazole is bound to plasma protein.

Tinidazole is excreted by the liver and kidneys. Studies in healthy patients have shown that over 5 days, 60-65% of an administered dose is excreted by the kidneys with 20-25% of the administered dose excreted as unchanged tinidazole. Up to 5% of the administered dose is excreted in the faeces.

Studies in patients with renal failure (creatinine clearance <22ml/min) indicate that there is no statistically significant change in tinidazole pharmacokinetic parameters in these patients, (see section 4.2).

5.3 Preclinical safety data

Lansoprazole

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction or genotoxicity.

In two rat carcinogenicity studies, lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids associated with hypergastrinaemia due to inhibition of acid secretion.

Intestinal metaplasia was also observed, as were Leydig cell hyperplasia and benign Leydig cell tumours. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.

In mouse carcinogenicity studies dose-related gastric ECL cell hyperplasia developed as well as liver tumours and adenoma of rete testis.

The clinical relevance of these findings is unknown.

Clarithromycin

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure, related to this toxicity, are not known in detail, but toxic doses were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a dose of 400 mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema.

No mutagenic effects were found in in vitro- and in vivo -studies with clarithromycin

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (i.v.) and x10 the clinical dose in monkey (p.o.) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was noted in rat studies. Cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/d. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).

Clarithromycin has been found in the milk of lactating animals.

In 3-day old mice and rats, the LD50 values were approximately half those in adult animals. Juvenile animals presented similar toxicity profiles to mature animals although enhanced nephrotoxicity in neonatal rats has been reported in some studies. Slight reductions in erythrocytes, platelets and leukocytes have also been found in juvenile animals.
Clarithromycin has not been tested for carcinogenicity.

Tinidazole

Repeat-dose toxicity

In a repeat-dose toxicity study in beagle dogs, oral administration of tinidazole increased atrophy of the thymus in both sexes at 300 and 600 mg/kg/day, and atrophy of the prostate in males at all doses of 100, 300 and 600 mg/kg/day. The initial highest dose of 1000 mg/kg/day was lowered to 600 mg/kg/day due to severe clinical signs. The no-observed-adverse-effect level for females was 100 mg/kg/day (approximately 0.9 times the highest human dose based upon plasma AUC).

Genotoxicity/carcinogenicity

Tinidazole showed some evidence of mutagenic potential. In an in vitro mutagenicity assay, tinidazole was mutagenic in the TA 100, S. typhimurium tester strain both 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.

Tinidazole carcinogenicity studies in rats, mice or hamsters have not been reported. However, metronidazole, a chemically-related nitroimidazole, has been reported to be carcinogenic in mice and rats but not hamsters. In several studies metronidazole showed evidence of pulmonary, hepatic, and lymphatic tumorigenesis in mice and mammary and hepatic tumours in female rats.

Reproductive and developmental toxicity

Tinidazole did not cause malformations in mice or rats. In rats, oral administration of tinidazole reduced embryo-foetal viability and growth retardation (reduced foetal weight and increased skeletal variations) from 500 mg/kg/day (approximately 2 times the highest human therapeutic dose based upon body surface area). In a rat developmental toxicity study, a higher incidence of foetal mortality was noted following oral administration of 600 mg/kg (approximately 3 times the highest human therapeutic dose based upon body surface area). Embryo-foetal toxicity was not observed in mice at the highest dose level of 2,500 mg/kg (approximately 6 times the highest human therapeutic dose based upon body surface area).

In a male rat fertility study, oral administration of tinidazole reduced fertility at 600 mg/kg/day. Degeneration of the seminiferous tubules in the testes with corresponding effects on spermatogenic measures were noted at 300 and 600 mg/kg/day. The NOAEL for testicular and spermatogenic effects was 100 mg/kg/day (approximately 0.5 times the highest human therapeutic dose based upon body surface area). In another study, oral administration of tinidazole reduced fertility in male rats at 300 mg/kg/day and in female rats at 150 and 300 mg/kg/day.

6. Pharmaceutical particulars

6.1 List of excipients

A. Lansoprazole Delayed Release Capsules USP 30 mg

Lansoprazole Pellets 11.20 %

Lansoprazole
Mannitol
Disodium hydrogen phosphate
Light magnesium carbonate
Calcium carboxy methyl cellulose
Starch
Sugar (Pharma grade)
Sugar spheres (#30-40)
Methylparaben sodium
Propylparaben sodium
Hydroxy propyl methyl cellulose (HPMC-E5)
Methacrylic acid copolymer (L-30D)
Sodium hydroxide
Diethyl phthalate
Talc
Titanium dioxide
Tween-80 (Polysorbate-80)
Polyvinyl povidone K-30
Cross carmelose sodium

EHGC Pink/ Clear Transparent Size 2:

Gelatin
Methylparaben sodium
Propylparaben sodium
Sodium Lauryl sulfate
Erythrosine
Purified water

B. Clarithromycin Tablets USP 250 mg

Sodium Lauryl Sulphate
Povidone (K-30)
Isopropyl Alcohol
Colloidal Silicon Dioxide
Crospovidone
Magnesium Stearate
Anhydrous Calcium Hydrogen Phosphate (Direct Compressible)
Hydroxy Propyl Methyl Cellulose
Titanium Dioxide
Methylene Chloride

C. Tinidazole Tablets 500 mg

Tablet Core:

Maize Starch
Microcrystalline Cellulose
Colloidal Silicon Dioxide
Sodium Starch Glycolate
Magnesium stearate
Colour Coat Sunset Yellow Organic (F/C)
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

None

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.
Keep all medicines out of reach of children.

6.5 Nature and contents of container

- 1 Alu-Pvc Blister of 4 tablets and 2 capsules to be packed in carton along with pack inert.
- Such 7 mono-cartons of Combikit to be packed in the one outer carton.

6.6 Special precautions for disposal and other handling

No Special Requirements.

7. MARKETING AUTHORISATION HOLDER

MORAF PHARMACEUTICALS LTD.
KIPANDE STREET,
KARIAKOO,
P.O. BOX 21323
DAR ES SALAAM, TANZANIA

Manufacturer
ZOTA HEALTH CARE
PLOT No 169, SURAT 94230
SPECIAL ECONOMIC ZONE, NEAR SACHIN RAILWAY STATION,
INDIA

8. MARKETING AUTHORISATION NUMBER(S)

TAN 22 HM 0485

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

05th December, 2022

10. DATE OF REVISION OF TEXT