SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
TRIO 1000 mg + 500 mg + 30 mg Therapy Package

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substance(s):
Each tablet contains amoxicillin trihydrate (from bovine, sheep or goat milk) equivalent to 1000 milligrams of amoxicillin base.
Each film-coated tablet contains 500 milligrams of clarithromycin.
Each enteric-coated micropellet capsule contains 30 milligrams of lansoprazole.
Excipient(s) with known effect:

Sucrose	200.949 mg
Tartrazine	0.972 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet. / Film-coated tablet. / Capsule.
Amoxicillin 1000 mg tablets are white to almost white, oblong tablets with DMS-1000 written on one side and a central notch on the other side.
Clarithromycin 500 mg film-coated tablets are yellow film-coated, homogeneous, rectangular (oblong) tablets with a central notch on one side.
Lansoprazole 30 mg capsules are micropellet opaque hard gelatin capsules (no. 1) with a cream-colored body and an orange cap, containing white to creamy-white pellets inside.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
The triple form of lansoprazole, amoxicillin and clarithromycin is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

4.2. Posology and method of administration
Posology/frequency and duration of administration:
The recommended adult dose is 30 mg lansoprazole, 500 mg clarithromycin and 1000 mg amoxicillin, all twice daily on an empty stomach (12 hours apart, morning and evening).
The recommended duration of administration is 7 to 14 days.

Method of administration:
Each medication should be swallowed undivided and with some liquid.

Additional information on special populations:
Renal impairment:
The use of the triple form of lansoprazole, amoxicillin and clarithromycin is not recommended in patients with creatinine clearance less than 30 mL/min.

Hepatic impairment:
Metabolism of lansoprazole is prolonged in severe hepatic impairment. Due to lansoprazole in TRIO Therapy Package, these patients should be kept under close observation and care should be taken not to exceed the daily dose of 30 mg. Dose reduction should be considered in patients with severe hepatic impairment.

Pediatric population:
The safety and efficacy of the triple form of lansoprazole, amoxicillin and clarithromycin in pediatric patients infected with *H. pylori* have not been established. Its use is therefore not recommended.

Geriatric population:
Elderly patients may have asymptomatic hepatic and renal impairment. Caution should be exercised when giving the triple form of lansoprazole, amoxicillin and clarithromycin to this patient group. Dose adjustment should be considered in patients with severe renal impairment.

4.3 . Contraindications
It is contraindicated in persons sensitive to the active substances in its formulation (amoxicillin, clarithromycin, and lansoprazole) and excipients, macrolide antibiotics, penicillin derivatives, cephalosporins.
The triple form of lansoprazole, clarithromycin and amoxicillin is contraindicated in combination with cisapride, pimozide, astemizole, ergotamine, dihydroergotamine or terfenadine (see section 4.5). It may cause long QT syndrome/Torsades de Pointes. Therefore, it should not be used in patients with diagnosed or suspected congenital prolonged QT syndrome or Torsades de Pointes.
The triple form of lansoprazole, clarithromycin and amoxicillin together with derivatives of ergot is contraindicated. Lansoprazole should not be taken with atazanavir (see section 4.5).
Clarithromycin is contraindicated in combination with any of the following drugs as it may cause QT prolongation and cardiac arrhythmias such as ventricular tachycardia, ventricular fibrillation and torsades de pointes: Astemizole, cisapride, pimozide and terfenadine.
Clarithromycin is contraindicated in combination with ergot alkaloids (e.g. ergotamine and dihydroergotamine) as it may cause ergot toxicity.
The concomitant use of clarithromycin with oral midazolam is contraindicated.
Clarithromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmias including Torsades de Pointes (see sections 4.4 and 4.5).
Clarithromycin should not be given to patients with hypokalemia (risk of QT interval prolongation).
Clarithromycin should not be used in patients with severe hepatic impairment together with renal impairment.
Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins; lovastatin or simvastatin), which are largely metabolized by CYP3A4, because of the risk of increased myopathy, including rhabdomyolysis.
Concomitant use of colchicine with clarithromycin (and other strong CYP3A4 inhibitors) is contraindicated in patients with renal or hepatic impairment (see sections 4.4. and 4.5.).

4.4. Special warnings and precautions for use
The triple form of lansoprazole, clarithromycin and amoxicillin should be used only for the stated indication and as directed. The drugs in this package, must not be used for other purposes, either separately or in combination.
The possibility of superinfection with mycotic organisms and bacterial pathogens should not be ruled out during treatment. In such cases, the triple form of lansoprazole, amoxicillin and clarithromycin should be discontinued and appropriate treatment initiated.

Clarithromycin
The use of any antimicrobial treatment, such as clarithromycin, to treat *H. pylori* infection can lead to an increase in drug-resistant organisms.
Clarithromycin should not be used in pregnant women, except in clinical situations where none of the other alternative treatments are appropriate. If pregnancy occurs while taking this drug, the patient should be informed of the potential harm to the fetus. Adverse effects of clarithromycin on gestational product and/or embryo-fetal development have been detected in monkeys, rats, mice and rabbits administered doses that produced plasma levels 2 to 17 times

the serum levels obtained in humans treated with the maximum recommended human doses (see section 4.6).
As seen in other antibiotics, long-term use leads to a rise in the number of non-susceptible bacteria and fungi. If superinfection occurs, appropriate therapy should be initiated.
Caution should be exercised in the concomitant use of clarithromycin and triazolobenzodiazepines such as triazolam and intravenous midazolam (see section 4.5).
Because of the risk of QT prolongation, caution should be exercised when clarithromycin is used concomitantly with coronary artery disease, severe heart failure, hypomagnesemia, bradycardia (<50 beats/min) or other medicinal products associated with QT prolongation (see section 4.5).
In a clinical trial evaluating the outcomes of treatment with clarithromycin in patients with coronary artery disease, an increased risk of all-cause mortality was observed one year or more after the end of treatment in patients randomized to receive clarithromycin. Clarithromycin is not indicated for the treatment of coronary artery disease. The reason for the increase in risk could not be determined. Other epidemiologic studies assessing this risk have reached variable conclusions. Patients with coronary artery disease or suspected coronary artery disease should undergo a risk-benefit assessment before using clarithromycin.
Clarithromycin should not be used in patients with a congenital or documented history of acquired QT prolongation or ventricular arrhythmias (see section 4.3 Contraindications).

Pseudomembranous colitis
Pseudomembranous colitis has been seen with almost all antibacterial agents, including macrolides, and can range in severity from mild to life-threatening. It is therefore important to consider this diagnosis in patients with diarrhea before administering antibacterial agents.
Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of almost all antibacterial agents, including clarithromycin, and the severity of diarrhea ranges from mild to fatal colitis. Treatment with antibacterial agents leads to changes in the normal flora of the colon, which can lead to the proliferation of C. difficile.
CDAD should be considered in all patients with diarrhea following antibiotic use. Reports of CDAD formation even more than 2 months after administration of antibacterial agents require a careful medical history. Treatment with antibacterial agents alters the normal flora of the large intestine and may cause overgrowth of clostridia. Studies have shown that a toxin produced by Clostridium difficile is the main cause of antibiotic-induced colitis.
Once pseudomembranous colitis has been diagnosed, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond only to drug withdrawal. Fluid, electrolyte treatment, protein supplementation and treatment with an antibacterial drug effective against Clostridium difficile colitis should be applied in moderate to severe cases.
Exacerbation of myasthenia gravis symptoms has been reported in patients receiving clarithromycin treatment.

Renal and hepatic impairment
Clarithromycin is mainly excreted by the liver. Caution should therefore be exercised when administering clarithromycin to patients with impaired liver function. Increased liver enzymes and hepatic dysfunction, including hepatocellular and/or cholestatic hepatitis with or without jaundice, have been reported with clarithromycin. This hepatic dysfunction can be severe and is usually reversible. In some cases, fatal hepatic failure has been reported and is usually associated with severe underlying disease and/or concomitant drug use. Clarithromycin should be stopped immediately if signs and symptoms of hepatitis such as anorexia, jaundice, dark urine, itching or abdominal tenderness occur.
Caution should be exercised in patients with moderate to severe renal impairment. However,

in cases of severe renal impairment, with or without concomitant hepatic impairment, dose reduction or prolongation of dose intervals may be appropriate.

Colchicine toxicity
When clarithromycin and colchicine are used concomitantly, there are reports of colchicine toxicity, especially in the elderly and some in patients with renal failure. Deaths have been reported in some of these patients (see section 4.5). In cases where clarithromycin and colchicine should be administered concomitantly, patients should be monitored for clinical signs of colchicine toxicity. The dose of colchicine should be reduced in all patients receiving colchicine and clarithromycin concomitantly. Administration of clarithromycin and colchicine concomitantly is contraindicated in patients with renal or hepatic failure (see section 4.3).

Macrolide antibiotics
The possibility of cross-resistance to clarithromycin as in the case of other macrolide antibiotics such as lincomycin and clindamycin should also be considered.
Caution should be exercised in the concomitant use of clarithromycin and other ototoxic drugs, especially aminoglycosides. Vestibular and hearing functions should be monitored during and after treatment.

Oral hypoglycemic agents/insulin
The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin may cause significant hypoglycemia. When used concomitantly with certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, clarithromycin may cause inhibition of the CYP3A enzyme and consequently hypoglycemia. In such cases, careful monitoring of glucose levels is recommended.

Oral anticoagulants
When clarithromycin is administered concomitantly with warfarin, there is a serious risk of hemorrhage and a significant increase in INR, prothrombin time. INR and prothrombin times should be checked frequently when patients are taking clarithromycin and anticoagulants concomitantly.

HMG-CoA reductase inhibitors (statins)
The concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated because these statins are largely metabolized by CYP3A4 and concomitant treatment with clarithromycin may increase plasma concentrations, increasing the risk of myopathy, including rhabdomyolysis (see section 4.3). Rhabdomyolysis has been reported in patients receiving clarithromycin concomitantly with these statins. If treatment with clarithromycin is unavoidable, treatment with lovastatin or simvastatin should be interrupted during treatment.
Caution should be exercised when prescribing clarithromycin together with statins. Where the concomitant use of clarithromycin with statins is unavoidable, it is recommended that the lowest registered dose of statin be prescribed. The use of statins that are not dependent on CYP3A metabolism (e.g. fluvastatin) may be considered.
Caution should be exercised when clarithromycin is used concomitantly with drugs that induce the cytochrome CYP3A4 enzyme (see section 4.5).

Pneumonia
Since Streptococcus pneumonia develops resistance to macrolides, it is important to perform susceptibility testing before giving clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with appropriate additional antibiotics.

Mild to moderate skin and soft tissue infections
These infections are often caused by Staphylococcus aureus and Streptococcus pyogenes, or both, which can develop resistance to macrolides. Sensitivity testing is therefore important. In cases where beta-lactam antibiotics cannot be used (e.g. due to allergy), other antibiotics such as clindamycin may be the first-line drug of choice. Currently, macrolides are thought to play a role only in infections caused by Corynebacterium minutissimum (erythrasma), some skin and soft tissue infections such as acne vulgaris and erysipelas, and in cases where penicillin treatment cannot be used.
In case of severe acute hypersensitivity reactions such as anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS and Henoch-Schonlein purpura, clarithromycin treatment should be discontinued immediately and appropriate treatment initiated.

Amoxicillin

Serious and rarely fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving penicillin treatment. Such reactions have been observed more frequently with parenteral administration than with oral administration, especially in people with sensitization to many allergens. Before starting penicillin treatment, a thorough investigation should be made to rule out any previous hypersensitivity reaction to penicillin, cephalosporins and other allergens. If an allergic reaction occurs, amoxicillin administration should be discontinued and appropriate treatment should be administered. Emergency treatment of severe anaphylactic reactions with adrenaline is essential. The airway should be kept open, including oxygen, intravenous steroid application and intubation if needed.

Cross-allergy to penicillins may also be reported in patients with reported hypersensitivity to cephalosporin group antibiotics.
During treatment with all antimicrobial agents, mild or severe pseudomembranous colitis has been reported. Therefore, diarrhea developing during treatment with amoxicillin should be evaluated in this respect. During treatment with antibacterial agents, the normal intestinal flora may be disrupted and this may lead to overgrowth of Clostridia group pathogens. The toxin produced by Clostridium difficile is the most important cause of antibiotic-associated colitis. In mild cases, discontinuation of treatment is sufficient, while in severe cases, fluid-electrolyte treatment and the use of an antibacterial agent against C. difficile are required.
Glandular fever associated with erythematous (morbilliform) rashes may be seen in patients receiving amoxicillin.
During treatment, the possibility of superinfection with bacterial pathogens *(Enterobacter, Pseudomonas*) and fungi *(Candida*) should not be ruled out. In such a case, the drug should be stopped and appropriate treatment started.
Prolonged use may cause overgrowth in non-sensitive organisms.
Patients with infectious mononucleosis have an increased risk of erythematous skin rash. Therefore, amoxicillin class antibiotics should not be used in patients with mononucleosis.
As with all potent drugs, it is recommended to monitor renal hepatic and hemapoietic functions during treatment.
Patients with gonorrhea should also be tested for syphilis and evaluated with a new test 3 months after the end of amoxicillin treatment.
In patients with decreased urine output, crystalluria may be observed very rarely, especially at high doses. It is recommended to increase fluid intake to prevent this.
In patients with impaired renal function, amoxicillin excretion is reduced in proportion to the degree of renal impairment. The dose of amoxicillin given may need to be reduced.
Serious and sometimes fatal hypersensitivity reactions (including anaphylactoid and severe

cutaneous reactions) have been reported in penicillin-treated patients. Hypersensitivity reactions can also progress to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in atopic individuals with a history of hypersensitivity to penicillin. If an allergic reaction occurs, amoxicillin treatment should be discontinued and appropriate alternative treatment initiated.
Drug-induced enterocolitis syndrome (DIES) has been reported mostly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction in which prolonged vomiting (1-4 hours after drug use) is the leading symptom in the absence of allergic skin and respiratory symptoms. Other symptoms include abdominal pain, diarrhea, hypotension or neutrophilic leukocytosis. Severe cases progressing to shock have been seen.
Crystalluria (including acute kidney injury) has occurred very rarely in patients with reduced urine output, especially with parenteral treatment. During high-dose amoxicillin treatment, it is advisable to take appropriate amounts of fluid and regulate the amount of urine to reduce the possibility of amoxicillin crystalluria. In patients with a bladder catheter, the patency of the catheter should be checked regularly (see sections 4.8 and 4.9).

Lansoprazole
Lansoprazole is metabolized and excreted mainly through the bile. Therefore, the pharmacokinetic profile of the drug may be affected by moderate to severe hepatic impairment, as in its administration to the elderly. Caution should be exercised when giving lansoprazole in patients with impaired hepatic function (see section 4.2). In severe hepatic impairment, doses higher than 30 mg per day should not be used. Lansoprazole should be used with caution in moderate to severe hepatic impairment (see sections 4.2. and 5.2.).
In the elderly, T_{max} and area under the curve (AUC) values are twice those of the young. In elderly patients, the initial starting dose does not need to be changed, but subsequent doses should not exceed 30 mg daily, unless extra acid suppression is required. Caution should be exercised when used in elderly patients with hepatic impairment.
A symptomatic response to treatment with lansoprazole does not necessarily mean that a gastric tumor is not present. Lansoprazole treatment may mask signs of gastric malignancy. Therefore, patients should be evaluated for the possibility of gastric malignancy before starting treatment.
A symptomatic response to treatment with lansoprazole does not necessarily mean that a gastric tumor is not present. Lansoprazole treatment may mask signs of gastric malignancy. Therefore, patients should be evaluated for the possibility of gastric malignancy before starting treatment.
Treatment with proton pump inhibitors may result in a slight increase in the risk of gastrointestinal infections such as *Salmonella* and *Camphylobacter* (see section 5.1).
In patients with gastro-duodenal ulcer complaints, the possibility of *H. pylori* infection as an etiologic factor should be considered.
If lansoprazole is used in combination with antibiotics for the treatment of *H. pylori* eradication, the product information of these antibiotics should also be followed.
As there are limited safety data for patients on maintenance treatment for more than one year, their treatment should be reviewed regularly and a comprehensive risk/benefit assessment should be performed.
Very rare cases of colitis have been observed in patients taking lansoprazole. Therefore, discontinuation of therapy should be considered in cases of severe and/or persistent diarrhea.
In the treatment of peptic ulcer, in high-risk patients with the need for continuous NSAID treatment (e.g., history of gastrointestinal bleeding, perforation or ulcer, advanced age, concomitant use with medications known to increase the likelihood of upper GI adverse

effects [e.g., corticosteroids or anticoagulants], presence of a serious concomitant disease factor, or prolonged use of maximum recommended doses of NSAIDs) must be controlled.

Bone fractures
Several published observational studies suggest that proton pump inhibitor (PPI) treatment may be associated with an increased risk of osteoporosis-related fractures of the hip, wrist or spine. Patients receiving high doses, defined as multiple daily doses and long-term PPI treatment (one year or more), are at increased risk of fracture. Patients should receive the lowest dose and shortest duration of PPI treatment appropriate for the condition for which they are being treated.

Hypomagnesemia
Symptomatic and asymptomatic hypomagnesemia has been reported rarely in patients treated with PPIs for at least 3 months and in most cases after one year of treatment. Serious adverse events include tetany, arrhythmias and seizures. In most patients, treatment of hypomagnesemia requires magnesium replacement and discontinuation of PPI treatment. For patients who are expected to receive long-term treatment or who are taking PPIs concomitantly with drugs such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals may monitor magnesium levels before starting PPI treatment and periodically thereafter.

Interactions with examinations for neuroendocrine tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. Increased CgA levels may lead to false positive results in diagnostic tests for neuroendocrine tumors. Administrators should temporarily interrupt PPI treatment before assessing CgA levels and repeat the test if baseline CgA levels are high. If serial tests are performed (e.g. for monitoring), the tests should be performed in the same laboratory as reference intervals between tests may vary.

Subacute cutaneous lupus erythematosus
Proton pump inhibitors have very rarely been associated with subacute cases of cutaneous lupus erythematosus. If lesions appear, particularly on sun-exposed areas of the skin, and are accompanied by arthralgia, the patient should seek medical attention urgently and the healthcare professional should consider discontinuation of lansoprozole treatment. The development of subacute cutaneous lupus erythematosus after previous treatment with a proton pump inhibitor increases the risk of developing the same condition with other proton pump inhibitors.

Excipient warnings
This medicinal product contains sucrose. Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not use this drug.
It contains lansoprazole sodium included in the TRIO Therapy Package. This should be considered in patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction
Amoxicillin
Bacteriostatic antibiotics such as chloramphenicol, macrolides, sulfonamides and tetracyclines can inhibit the bactericidal activity of penicillins. This interaction has been established in vitro, but its clinical significance has not been fully demonstrated.

Methotrexate
Penicillins may reduce the excretion of methotrexate, potentially leading to a rise in toxicity.

Probenecid
Concomitant use with probenecid is not recommended. Probenecid may decrease renal tubular secretion of amoxicillin. Concomitant use with probenecid may result in increased blood levels and prolonged stay of amoxicillin in the blood.
Amoxicillin, like other antibiotics, affects the intestinal flora and decreases the absorption of estrogen. It may reduce the effectiveness of combined oral contraceptives.
Concomitant administration with allopurinol increases the risk of allergic skin reactions.
Concomitant use with anticoagulants is known to prolong prothrombin time. If taken together, there should be appropriate monitoring.
Prolongation of prothrombin time may rarely be observed in patients receiving amoxicillin. Appropriate monitoring is advised when administered in combination with anticoagulants.
When urine glucose is examined, it is recommended to use enzymatic glucose oxidase methods. False positive results can be obtained by chemical methods.
Temporary decreases in total conjugated esTRIOl, esTRIOl glucronide, conjugated estrone and estrodiol levels may be observed during use in pregnant women.

Clarithromycin
The use of the following drugs is contraindicated due to serious drug interactions.

Cisapride, pimozide, astemizole and terfenadine:
Elevated levels of cisapride have been seen in patients taking cisapride concomitantly with clarithromycin. This can result in QT interval widening and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes, especially in cardiac patients. Similar effects were seen in patients using clarithromycin and pimozide concomitantly (see section 4.3).
Macrolides have been reported to increase terfenadine levels by affecting terfenadine metabolism, resulting in cardiac arrhythmias such as QT interval widening, ventricular tachycardia, ventricular fibrillation and Torsades de Pointes (see section 4.3.). In a study of 14 volunteers, concomitant administration of clarithromycin and terfenadine resulted in a 2/3-fold increase in the blood level of the acid metabolite of terfenadine and QT interval prolongation with no detectable clinical effects. Similar effects were seen with concomitant administration of astemizole and other macrolides.

Ergot alkaloids:
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine is associated with acute ergot toxicity characterized by vasospasm and ischemia in the limbs and other tissues, including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated (see section 4.3).

Etravirine:
Clarithromycin exposure was reduced with etravirine; however, the concentration of the active metabolite 14-OH-clarithromycin increased. Since 14-OH-clarithromycin reduces activity against mycobacterium avium complex (MAC), overall activity against this pathogen may vary; thus, alternatives to clarithromycin should be considered for the treatment of MAC.

Effects of other drugs on the clarithromycin
CYP3A inducing drugs:

CYP3A inducing drugs (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort) may increase clarithromycin metabolism. This may result in subtherapeutic levels of clarithromycin leading to reduced efficacy. It may also be necessary to monitor the plasma level of the CYP3A inducer; the level of this drug may increase due to CYP3A inhibition by clarithromycin (see product information for the CYP3A4 inducer used). In the concomitant use of rifabutin and clarithromycin, rifabutin serum levels increase while clarithromycin serum levels decrease, leading to an increased risk of uveitis.
Following drugs are known or suspected effects on circulating clarithromycin concentrations; clarithromycin dose adjustment or switch to alternative treatment may be necessary.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine:
Potent stimulants of the cytochrome P450 metabolism system, such as efavirenz, nevirapine, rifampicin, rifabutin and rifapentine, can accelerate the metabolism of clarithromycin, thereby increasing the microbiologically active 14(R)-hydroxy-clarithromycin (14-OH-clarithromycin) and decreasing plasma levels of clarithromycin. The microbiological activities of clarithromycin and 14-OH-clarithromycin differ for different bacteria. Concomitant administration of enzyme stimulants with clarithromycin may impair the intended therapeutic activity.

Fluconazole: In healthy volunteers, concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily increased the mean steady-state Cmin and AUC of clarithromycin by 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin are not significantly affected by concomitant administration with fluconazole. 21 healthy volunteers received fluconazole 200 mg/day plus clarithromycin 500 mg/day twice. The mean steady-state minimum concentration (C_{min}) and area under the curve (AUC) of clarithromycin were 33% and 18%, respectively. Steady-state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration with fluconazole. Clarithromycin does not require dose adjustment.

Ritonavir: A pharmacokinetic study in which 200 mg ritonavir every 8 hours was administered concomitantly with 500 mg clarithromycin every 12 hours resulted in a significant inhibition of clarithromycin metabolism. Concomitant administration with ritonavir increased clarithromycin C_{max} by 31%, C_{min} by 182% and AUC by 77%. 14-[R]-hydroxyclarithromycin formation was completely inhibited. Due to the wide therapeutic window of clarithromycin, there is no need to reduce the dose in patients with normal renal function. However, the following dose adjustment should be made in patients with renal impairment: Clarithromycin dose should be reduced by 50% in patients with CLCR 30-60 mL/min. In patients with CLCR <30 mL/min, the dose should be reduced by 75%. Clarithromycin doses higher than 1 g per day should not be administered concomitantly with ritonavir (see section 4.2).
Similar dose adjustments should be considered when used concomitantly with other HIV protease inhibitors such as ritonavir, atazanavir and saquinavir as a pharmacologic enhancer in patients with reduced renal function (see section Drug-Drug Interactions).

Effects of clarithromycin on other drugs
Antiarrhythmics
There are postmarketing reports indicating Torsades de Pointes with concomitant use of clarithromycin with quinidine or disopyramide. Patients should be monitored with electrocardiograms for QTc prolongation during concomitant administration of clarithromycin

with these drugs. Serum levels of these drugs should be monitored during clarithromycin treatment.

CYP3A-induced interactions
Concomitant administration of clarithromycin, which is known to inhibit CYP3A, and a drug that is metabolized primarily by CYP3A may result in increases in the concentrations of these drugs that may lead to an increase or prolongation of both therapeutic and adverse effects. Particularly if the CYP3A substrate has a narrow safety margin (e.g. carbamezapine) and/or the substrate is extensively metabolized by this enzyme, it should be used with caution in patients receiving other drug treatments. If possible, serum concentrations of drugs primarily metabolized by CYP3A should be closely monitored in patients receiving clarithromycin and dose adjustment should be considered. The following drugs or classes of drugs are known or suspected to be metabolized by the same CYP3A isozyme: Alfentanil, bromocriptine, alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam, vinblastine, phenytoin, hexobarbital, theophylline and valproate. This list could be more comprehensive.

Theophylline, carbamazepine
Clinical studies have shown that concomitant administration of theophylline and carbamazepine with clarithromycin resulted in a moderate but statistically significant ($P \leq 0.05$) increase in blood levels of these drugs. The dose may need to be reduced.

Omeprazole: In healthy adults, concomitant administration of 500 mg clarithromycin and 40 mg omeprazole every 8 hours increased steady-state plasma concentrations of omeprazole (C_{max}, AUC_{0-24} and $T_{1/2}$ by 30%, 89% and 34%, respectively). The mean 24-hour gastric pH was 5.2 when omeprazole was given alone and 5.7 when given concomitantly with clarithromycin.

Ranitidine bismuth citrate: Although clinically insignificant, concomitant administration of ranitidine bismuth citrate and clarithromycin resulted in increased plasma concentrations of ranitidine, bismuth and 14-hydroxyclarithromycin.

Sildenafil, tadalafil and vardenafil:
Each of the phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A and CYP3A can be inhibited by concomitant administration of clarithromycin. Concomitant administration of clarithromycin with sildenafil, tadalafil or vardenafil may lead to increased phosphodiesterase inhibitor exposure. When clarithromycin is given together with sildenafil, tadalafil and vardenafil, consideration should be given to reducing the dose of these drugs.

Tolterodine:
The primary route of metabolism of tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, the metabolism pathway identified for a subgroup of the population lacking CYP2D6 is via CYP3A. Inhibition of CYP3A in this population subgroup leads to significantly higher serum tolterodine concentrations. A reduction in the dosage of tolterodine may be necessary in the presence of CYP3A inhibitors, for example the use of clarithromycin in the CYP2D6 poorly metabolizing population.

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)
When midazolam was given together with clarithromycin tablets (500 mg/twice a day), the

AUC of midazolam increased 2.7-fold after intravenous administration and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is given with clarithromycin, the patient should be closely monitored for dose adjustment. The same precautions should be applied for other benzodiazepines metabolized by CYP3A. For benzodiazepines that are not dependent on CYP3A for elimination (temazepam, nitrazepam, lorazepam), there is no clinically relevant interaction with clarithromycin. Drug interactions and central nervous system (CNS) effects (e.g. sleepiness and confusion) have been reported in the concomitant use of clarithromycin and triazolam during postmarketing period. Monitoring of patients for increased CNS pharmacologic effects is recommended.

Interactions with other drugs

Colchicine: Colchicine is a substrate of 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 concomitantly, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity. When colchicine is administered with clarithromycin in patients with normal renal and hepatic function, the colchicine dose should be reduced. Administration of clarithromycin and colchicine concomitantly is contraindicated in patients with renal or hepatic impairment (see sections 4.3. and 4.4.).

Digoxin: Digoxin is thought to be a substrate for P-glycoprotein (Pgp), an efflux transporter. Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered concomitantly, the inhibition of Pgp by clarithromycin leads to an increase in digoxin exposure. Increased serum digoxin concentrations in patients receiving digoxin concomitantly with clarithromycin have been reported in post-marketing surveillance studies. Clinical findings consistent with digoxin toxicity, including potentially fatal arrhythmias, have been observed in some patients. Serum digoxin concentrations should be carefully monitored when patients use digoxin and clarithromycin together.

Zidovudine: Continuous oral administration of clarithromycin and zidovudine in HIV-infected adults may result in decreased steady-state levels of zidovudine. Since clarithromycin inhibits the absorption of concomitantly administered oral zidovudine, this interaction can be prevented by using clarithromycin and zidovudine doses 4 hours apart. This interaction has not been observed in pediatric HIV-infected patients receiving clarithromycin suspension concomitantly with zidovudine or dideoxinosine. This interaction is unlikely when clarithromycin is administered by intravenous infusion.

Phenytoin and valproate: There are spontaneous or published reports of interactions between CYP3A inhibitors, including clarithromycin, and drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). It is advised to determine serum levels when these drugs are used together with clarithromycin. Increased serum levels were reported.

There are no in-vivo human data on the interaction of clarithromycin with the following drugs: aprepitant, eletriptan, halofantrine and ziprasidone. However, since in vitro data suggest that these drugs are CYP3A substrates, caution should be exercised in the concomitant administration of clarithromycin with these drugs. Eletriptan should not be administered concomitantly with CYP3A inhibitors such as clarithromycin.
There were spontaneous or published interaction reports between CYP3A inhibitors including clarithromycin and cyclosporine, tacrolimus, methylprednisolone, vinblastine and cilostazol.

Drug-drug interactions

Atazanavir

Clarithromycin and atazanavir are both substrates and inhibitors of CYP3A and there is evidence for a drug-drug interaction. Co-administration of clarithromycin (500 mg/twice a day) with atazanavir (400 mg/once a day) leads to a 2-fold increase in clarithromycin exposure and a 70% decrease in 14-OH clarithromycin exposure and a 28% increase in atazanavir AUC. Due to the wide therapeutic window of clarithromycin, dose reduction is not required in patients with normal renal function. In patients with moderate renal function (creatinine clearance 30-60 mL/min), the clarithromycin dose should be reduced by 50%. In patients with creatinine clearance <30 mL/min, the clarithromycin dose should be reduced by 75% using the appropriate clarithromycin formulation. Clarithromycin in daily doses higher than 1000 mg should not be given in combination with protease inhibitors.

Calcium channel blockers

Due to the risk of hypotension, caution should be exercised when clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) are administered concomitantly. Plasma concentrations of clarithromycin and calcium channel blockers may increase due to interaction. Hypotension, bradyarrhythmia and lactic acidosis were observed in patients receiving clarithromycin and verapamil concomitantly.

Itraconazole

Clarithromycin and itraconazole are both substrates and inhibitors of CYP3A, leading to a drug-drug interaction. Clarithromycin may increase plasma levels of itraconazole, while itraconazole may increase plasma levels of clarithromycin.

Patients receiving itraconazole and clarithromycin concomitantly should be monitored closely for signs of increased or prolonged pharmacological effects.

Saquinavir

Clarithromycin and saquinavir are both substrates and inhibitors of CYP3A and there is evidence for a drug-drug interaction.

Clarithromycin (500 mg/twice a day) and saquinavir (soft gel capsules, 1200 mg/3 times a day) were administered concomitantly to 12 healthy volunteers. The mean steady-state area under the curve (AUC) and minimum concentration (C_{min}) of saquinavir were found to be 177% and 187% higher than those of saquinavir monotherapy. Clarithromycin AUC and C_{max} values were found to be approximately 40% higher than clarithromycin alone. If both drugs are administered concomitantly for a limited time at the doses/formulations studied, no dose adjustment is required. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects of saquinavir in hard gelatin capsules. Observations in drug interaction studies of saquinavir treatment alone may not be representative of the effects of saquinavir/ritonavir treatment. When saquinavir is given concomitantly with ritonavir, the potential effects of ritonavir on clarithromycin should be considered (see Precautions, Drug Interactions).

Didanosine

In HIV-infected adult patients, concomitant administration of Klacid tablets with didanosine did not result in a statistically significant change in didanosine pharmacokinetics.

Lansoprazole

Effects of lansoprazole on other drugs

Drugs whose absorption is pH dependent

Because lansoprazole causes a profound and prolonged inhibition of gastric acid secretion, it

may interfere with the absorption of drugs where gastric pH is critical for bioavailability.

Atazanavir: In a study, concomitant administration of lansoprazole (60 mg daily) with 400 mg atazanavir caused a significant reduction in atazanavir exposure in healthy volunteers (approximately 90% reduction in AUC and C_{max} values). Lansoprazole should not be administered concomitantly with atazanavir (see section 4.3.).

Ketoconazole and itraconazole: Absorption of ketoconazole and itraconazole from the gastrointestinal tract is increased in the presence of gastric acid. Since the use of lansoprazole may lead to sub-therapeutic concentrations of ketoconazole and itraconazole, the combination should be avoided.

Digoxin: Lansoprazole and digoxin together may lead to an increase in digoxin plasma levels. Therefore, digoxin plasma levels should be monitored during initiation and discontinuation of treatment with lansoprazole and the digoxin dose should be adjusted if needed.

Drugs metabolized by P450 enzymes
Lansoprazole may increase plasma concentrations of drugs metabolized by CYP3A4. Caution should be exercised in the concomitant use of lansoprazole with drugs that are metabolized by this enzyme and have a narrow therapeutic area.

Theophylline: Lansoprazole may reduce the expected clinical effect of theophylline at that dose by decreasing its plasma concentration. Caution should be exercised during concomitant use of these two drugs.

Tacrolimus: Concomitant use with lanzoprazole increases plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Lansoprazole exposure increases the average exposure to tacrolimus by up to 81%. It is recommended to monitor plasma concentrations of tacrolimus when initiating or discontinuing concomitant treatment with lansoprazole.

Drugs transported by P-glycoprotein
Lansoprazole has been observed to inhibit the transporter protein P-glycoprotein (P-gp) in vitro. The clinical relevance of this is unknown.

Effects of other drugs on lansoprazole
Drugs that inhibit CYP2C19
Fluvoxamine: Dose reduction should be considered during concomitant use of lansoprazole with CYP2C19 inhibitor fluvoxamine. Lansoprazole plasma concentrations rise up to 4-fold.

Drugs that induce CYP2C19 and CYP3A4
Rifampicin and enzyme inducers affecting CYP2C19 or CYP3A4, such as St. John's wort (Hypericum perforatum), may markedly reduce serum concentrations of lansoprazole.

Others
Sucralfate/Antacids: Sucralfate/Antacids may decrease the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least 1 hour after the use of these drugs. In clinical trials, antacids were used in combination with lansoprazole and there was no evidence of a change in the effectiveness of lansoprazole.
There are no clinical studies showing a significant interaction of lansoprazole with NSAIDs.
In a study in healthy subjects, concomitant administration of warfarin and 60 mg lansoprazole in single or multiple doses did not alter warfarin pharmacokinetics or prothrombin time. However, increases in INR and prothrombin time have been reported in some patients using

proton pump inhibitors and warfarin together. Increases in INR and prothrombin time can lead to abnormal bleeding and even death. Patients using proton pump inhibitors and warfarin together may need to be monitored for possible increases in INR and prothrombin time.

Additional information on special populations
No interaction studies have been conducted with all three drugs.

Pediatric population
No interaction studies have been conducted with all three drugs.

4.6. Pregnancy and lactation
General advice
Pregnancy category is "C".

Women of childbearing potential / contraception
The active ingredient amoxicillin in the triple form of lansoprazole, clarithromycin, amoxicillin may alter the absorption of estrogen-containing oral contraceptives, as may be the case with all antibiotics. Therefore, an alternative effective and reliable contraceptive method can be used during treatment.

Pregnancy
Safety of the triple form of lansoprazole, clarithromycin and amoxicillin in pregnant women has not been established. Triple form of lansoprazole, clarithromycin and amoxicillin should be used in pregnant women only when the potential benefit outweighs the potential risk.
Data on a large number of cases of exposure to amoxicillin during pregnancy do not indicate that amoxicillin has adverse effects on pregnancy or on the health of the fetus/newborn child.
There are insufficient data on the use of lansoprazole in pregnancy. No teratogenic effect was observed in animal studies.
However, clarithromycin should not be used in pregnant women except in clinical situations where none of the other alternative treatments are appropriate. If pregnancy occurs while taking this drug, the patient should be informed of the potential harm to the fetus.

Breast-feeding
Clarithromycin and amoxicillin are excreted in breast milk. Lansoprazole and its metabolites have been found to pass into breast milk in experimental animals, but it is not known whether they pass into human breast milk. In view of the potential for serious side effects in breast-feeding infants, the decision to discontinue treatment with triple form of lansoprazole, clarithromycin and amoxicillin in a breast-feeding mother or to discontinue breast-feeding should be based on the benefit of treatment for the mother.

Fertility
Animal studies did not reveal any adverse effects on fertility. No human studies are available.

4.7. Effects on ability to drive and use machines
There are no data on the effect of triple form of lansoprazole, clarithromycin and amoxicillin on driving and using machines. Since dizziness, vertigo, confusion and disorientation may occur with clarithromycin, this should be taken into account before driving or using machines.

4.8. Undesirable effects
The side effects seen in the treatment using the triple form of lansoprazole, clarithromycin and amoxicillin are listed below by systems and frequency: 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 (cannot be estimated from the available data).

Nervous system disorders
Common: Headache (6%);
Not known*: Confusion, dizziness;

Respiratory, thoracic and mediastinal disorders
Common: Respiratory disorders;

Gastrointestinal disorders
Common: Diarrhea (7%), taste disturbance (5%),
Not known*: Abdominal pain; dark feces, dry mouth, thirst, glossitis, rectal itching, oral moniliasis, stomatitis, tongue discoloration, tongue dysfunction, vomiting

Skin and subcutaneous tissue disorders
Not known*: Skin reactions

Musculoskeletal, connective tissue and bone disorders
Not known*: Myalgia;

Reproductive system disorders:
Not known*: Vaginitis; vaginal moniliasis.
* These side effects are seen in less than 3% of patients

Clarithromycin
Infections and infestations
Uncommon: Candidiasis, vaginal infection
Not known: Pseudomembranous colitis, erysipelas, erythrasma

Blood and lymphatic system disorders
Uncommon: Leukopenia, neutropenia, eosinophilia
Not known: Agranulocytosis, thrombocytopenia

Immune system disorders
Uncommon: Hypersensitivity
Not known: Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon: Anorexia, decreased appetite
Not known: Hypoglycemia

Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety
Not known: Psychotic disorder, confusional state, depersonalization, depression, disorientation, hallucinations, abnormal dreams, mania

Nervous system disorders
Common: Dysphagia, headache, change in taste
Uncommon: Dizziness, tremor
Not known: Convulsions, ageusia, parosmia, anosmia, paresthesia

Ear and labyrinth disorders
Uncommon: Vertigo, hearing impairment, tinnitus
Not known: Deafness

Cardiac disorders
Uncommon: Prolonged QT, palpitations on electrocardiogram
Not known: Torsades de pointes, ventricular tachycardia

Vascular disorders
Not known: Haemorrhage

Gastrointestinal disorders
Common: Diarrhea, vomiting, dyspepsia, nausea, abdominal pain
Uncommon: Gastritis, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence
Not known: Acute pancreatitis, tongue discoloration, tooth discoloration

Hepatobiliary disorders
Common: Abnormal liver function tests
Uncommon: Cholestasis, hepatitis, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma glutamyl transferase
Not known: Hepatic failure, hepatocellular jaundice

Skin and subcutaneous tissue disorders
Common: Rash, hyperhidrosis
Uncommon: Pruritus, urticaria
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Henoch-Schonlein purpura

Musculoskeletal, connective tissue and bone disorders
Not known: Myopathy

Renal and urinary disorders
Not known: Renal failure, interstitial nephritis

General
Uncommon: Weakness, asthenia, chest pain, chills, fatigue

Investigations
Uncommon: Blood alkaline phosphatase increased, blood lactate dehydrogenase increased
Not known: Increased international normalized ratio, prolonged prothrombin time, abnormally colored urine

Changes in laboratory values: Laboratory changes that may have clinical significance include the following: SGPT (ALT) increased (<1%), SGOT (AST) increased (<1%), GGT increased (<1%), alkaline phosphatase increased (<1%), LDH increased (<1%), total bilirubin increased (<1%), white blood cells decreased (<1%), prolonged prothrombin time (1%), BUN

increased (4%), serum creatinine increased (<1%).

Side effects in immunocompromised patients:
In immunocompromised patients treated with high doses of clarithromycin for mycobacterial infections for prolonged periods of time, it is often difficult to distinguish side effects possibly related to clarithromycin administration from the underlying symptoms of HIV disease or progressive disease.
The most commonly reported adverse reactions by adult patients treated with a total daily dose of 1000 mg and 2000 mg clarithromycin: Nausea, vomiting, taste changes, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing impairment, elevated SGOT and SGPT. Less frequent dyspnea, insomnia and dry mouth have been reported. While there was no difference in incidence between 1000 mg and 2000 mg treatment, the incidence increased 3-4 fold in 4000 mg clarithromycin daily treatment.
In these immunocompromised patients, laboratory values that were outside the highest or lowest level of the test were analyzed. According to this analysis, SGOT and SGPT levels were found to be elevated and white blood cell and platelet counts were found to be lower than normal in approximately 2-3% of patients using 1000 mg or 2000 mg clarithromycin daily. Blood urea nitrogen was less elevated in these two treatment groups. The incidence was slightly higher in the 4000 mg daily dose group for all parameters except white blood cells.

Amoxicillin
Infections and infestations
Very rare: Mucocutaneous candidiasis

Blood and lymphatic system disorders
Very rare: Hemolytic anemia, reversible thrombocytopenia, reversible leukopenia (severe neutropenia or agranulocytosis), prolonged bleeding time and prothrombin time (see section 4.5).

Not known: Anemia, thrombocytopenic purpura, eosinophilia and agranulocytosis have been reported. It is thought that these symptoms, which improve with discontinuation of the drug, may be due to a hypersensitivity reaction.

Immune system disorders
Very rare: Anaphylaxis, angioneurotic edema
Not known: Serum sickness-like reactions

Nervous system disorders
Very rare: Hyperkinesia, dizziness, convulsions. Convulsions may occur in patients with renal impairment or in patients receiving high doses.
Not known: Aseptic meningitis

Cardiac disorders
Not known: Kounis syndrome

Gastrointestinal disorders
Common: Nausea, diarrhea
Uncommon: Vomiting
Very rare: Black hairy tongue and hemorrhagic/pseudomembranous colitis

Not known: Drug-induced enterocolitis syndrome (DIES)

Hepatobiliary disorders
Very rare: Although a mild increase in SGOT has been reported, its clinical significance is not known.
Not known: Hepatic dysfunctions such as cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis

Skin and subcutaneous tissue disorders
Common: Skin rash
Uncommon: Urticaria and itching
Very rare: Skin reactions such as erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) (see section 4.4) and drug reaction with eosinophilia and systemic symptoms (DRESS).
Not known: Linear Ig A disease

Renal and urinary disorders
Very rare: Interstitial nephritis, crystalluria
Not known: Crystalluria (including acute kidney injury)

Other
Very rare: Discoloration of teeth (brown, yellow or grey staining) has rarely been reported. It can be removed by brushing and cleaning the teeth. They are mostly seen in children.

Lansoprazole
In general, lansoprazole is well tolerated by patients during short-term and long-term treatment. Side effects that may be related to lansoprazole in short-term treatment and that occurred in 1% or more of patients included diarrhea (3.6%) or constipation (1%), abdominal pain (1.8%), nausea (1.4%) and headache (>1%).
The most common side effect during maintenance treatment is diarrhea.

Blood and lymphatic system disorders
Uncommon: Thrombocytopenia, eosinophilia, leukopenia
Rare: Anemia
Very rare: Agranulocytosis, pancytopenia

Metabolism and nutrition disorders:
Not known: Hypomagnesemia (see section 4.4)

Psychiatric disorders
Uncommon: Depression
Rare: Insomnia, hallucinations, confusion

Nervous system diseases:
Common: Headache, dizziness
Rare: Restlessness, vertigo, paresthesia, somnolence, tremor

Eye disorders:
Rare: Vision disturbances

Gastrointestinal disorders
Common: Nausea, diarrhea, abdominal pain, constipation, vomiting, flatulence, dry mouth or throat, fundic gland polyps (benign)
Rare: Glossitis, esophageal candidiasis, pancreatitis, taste disorders
Very rare: Colitis, stomatitis

Hepatobiliary disorders
Common: Increased liver enzyme levels
Rare: Hepatitis, jaundice

Skin and subcutaneous disorders:
Common: Urticaria, itching, redness
Rare: Petechiae, purpura, hair loss, erythema multiforme, photosensitivity
Very rare: Stevens Johnson syndrome, toxic epidermal necrolysis
Not known: Subacute cutaneous lupus erythematosus (see section 4.4)

Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, myalgia, fracture of the hip, wrist or spine (see section 4.4)

Renal and urinary disorders
Rare: Interstitial nephritis

Reproductive system and breast disorders
Rare: Gynecomastia

General disorders and administration site conditions
Common: Fatigue
Uncommon: Edema
Rare: Fever, hyperhidrosis, anorexia, impotence and angioedema
Very rare: Anaphylactic shock

Investigations
Uncommon: Increased cholesterol and triglyceride levels, hyponatremia

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 via the national reporting system.

4.9. Overdose
If overdosed, patients should contact their doctor immediately. There is no pharmacologic evidence of an increased risk of toxicity with concomitant intake of all three drugs.

Clarithromycin: Excessive intake of clarithromycin can be expected to produce gastrointestinal symptoms. A patient with a history of bipolar disorder received 8 g clarithromycin and showed altered mental status, paranoid behavior, hypokalemia and hypoxemia. Allergic reactions accompanying overdose should be controlled by appropriate

elimination of the unabsorbed drug and supportive treatment. As with other macrolides, clarithromycin plasma levels are not affected by hemodialysis and peritoneal dialysis.

Lansoprazole: In cases of suspected overdose, the patient should be kept under observation. Lansoprazole cannot be removed from the circulation by hemodialysis. If necessary, gastric lavage, activated charcoal and symptomatic treatment are recommended.
Effects of lansoprazole overdose on humans (although acute toxicity is low) are not known, therefore no instruction for its therapy can be given. However, studies have used lansoprazole orally up to 180 mg and intravenously up to 90 mg with no significant adverse effects.
See section 4.8 for possible symptoms of lansoprazole overdose.
In one reported case of overdose, a patient receiving 600 mg lansoprazole showed no adverse effects. No deaths or clinical signs were observed as a result of oral lansoprazole doses up to 5000 mg/kg [approximately 1300 times the human dose of 30 mg based on body surface area (BSA)] in rats and 5000 mg/kg (approximately 675.7 times the human dose of 30 mg based on BSA) in mice.

Amoxicillin: Interstitial nephritis and crystalluria resulting in oliguric renal failure have been reported in a small number of patients. It was reversed with discontinuation of the drug.
In case of overdose, treatment should be discontinued and necessary symptomatic and supportive treatment should be administered. If recognized within a short period of time and there are no contraindications, the patient may be induced to vomit or be given gastric lavage. Amoxicillin is removed from the circulation by hemodialysis.
In some cases, amoxicillin crystalluria leading to renal failure were observed (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Combinations for eradication of *Helicobacter pylori*
ATC code: A02BD07

Lansoprazole, clarithromycin and/or amoxicillin were shown to be active against many strains of *Helicobacter pylori* in vitro and in clinical infections listed in the indications section.
Patients in whom H. pylori is not eradicated after treatment with triple form of clarithromycin, lansoprazole and amoxicillin are likely to have clarithromycin-resistant *H. pylori*. Therefore, clarithromycin susceptibility testing should be performed whenever possible in patients who do not respond to treatment. Patients infected with clarithromycin-resistant *H. pylori* should not be administered clarithromycin/lansoprazole/amoxicillin triple treatment or other treatments that include clarithromycin as the sole antibiotic.

Pharmacodynamic properties of lansoprazole:

Lansoprazole is a gastric proton pump inhibitor. It inhibits the activation of the H+/K+ -ATPase enzyme of gastric parietal cells, preventing the final step of gastric acid formation. Inhibition is dose-dependent and reversible, affecting both basal and stimulated gastric acid secretion. Lansoprazole is concentrated in parietal cells and is activated in acidic environments. It then reacts with the sulfhydryl group of the enzyme H+/K+ - ATPase causing inhibition of enzyme activity.

Effect on gastric acid secretion:

Lansoprazole is a selective parietal cell proton pump inhibitor. A single oral dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by up to 80%. It results with approximately 90% inhibition of gastric acid secretion after repeated daily administration for seven days. There is a reciprocal effect on basal secretion of gastric acid. A single dose of 30 mg reduces basal secretion by up to 70% and the patient's symptoms are regularly relieved starting from the initial dose. After eight days of repeated application, the reduction is approximately 85%. Rapid relief of symptoms is achieved with a single daily capsule (30 mg) and most patients with duodenal ulcers heal within 2 weeks and most patients with gastric ulcers and reflux esophagitis heal within 4 weeks. Lansoprazole decreases gastric acidity and creates conditions in which the appropriate antibiotic can be effective against *H. pylori*.

Decreased gastric acidity from any cause, including lansoprazole, leads to an increase in the number of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may slightly increase the risk of gastrointestinal infections such as *Salmonella* and *Camphylobacter* and possibly also *Clostridium difficile* in hospitalized patients.

Amoxicillin is an ampicillin analogue, semi-synthetic, broad-spectrum penicillin with bactericidal activity against Gram-positive and Gram-negative organisms.

Mechanism of action

Similar to ampicillin, it shows bactericidal effect by inhibiting the synthesis of bacterial cell wall mucopeptides during active division.

Microorganisms it is effective against:

Aerobic Gram-positive bacteria: *Enterococcus feacalis*, *those grow with susceptible Staphylococcal* species of group A beta-haemolytic *Streptococci* and *S. pneumonia* species, *Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus* (only penicillin-susceptible strains), *Corynebacterium species, Bacillus anthracis, Listeria monocytogenes, staphylococci susceptible to amoxicillin but resistant to methicillin/oxacillin should also be considered resistant to amoxicillin*.

Aerobic Gram-negative bacteria: *Escherichia coli* (strains not secreting beta-lactamase), *Haemophilus influenzae* (strains not secreting beta-lactamase), *Neisseria gonorrhoeae* (strains not secreting beta-lactamase), *Proteus mirabilis* (strains not secreting beta-lactamase), *Salmonella* species, *Shigella* species, *Bordetella pertussis, Brucella species, Neisseria gonorrhoeae, Neisseria meningitidis, Vibrio cholera, Pasteurella septica*

Helicobacter: *Helicobacter pylori*

Anaerobic bacteria: Clostridium species

Pharmacodynamic properties of clarithromycin:
Clarithromycin is a semi-synthetic macrolide antibiotic.
Mode of action: Clarithromycin exerts its antibacterial effect by binding to the ribosomal 50S subunit, which inhibits protein synthesis. The 14-OH metabolite of clarithromycin is twice as active against some organisms as the parent molecule.

Microbiology

Clarithromycin shows excellent in vitro activity against standard bacterial strains and clinical isolates. It has a high potential against a wide range of aerobic and anaerobic Gram positive and Gram negative organisms. The minimum inhibitory concentrations (MIC) of clarithromycin are generally one log2 dilution more potent than the MICs of erythromycin.

In vitro data show that clarithromycin also has excellent activity against *Legionella pneumophila* and *Mycoplasma pneumoniae*. It is also effective against Mycobacterium avium complex (MAC) organisms. It shows bactericidal effect against *Helicobacter pylori*. This effect of clarithromycin is stronger at neutral pH than at acidic pH. *In vitro* and *in vivo* data show that this antibiotic has activity against clinically important mycobacterial species. *In vitro* data suggest that *Enterobacteriaceae*, pseudomonas species and other Gram-negative bacilli that do not ferment lactose are not susceptible to clarithromycin.

Clarithromycin has been shown to be effective against most strains of the following organisms, both in vitro and in clinical infections:

Gram-positive aerobes: *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Listeria monocytogenes*.

Gram-negative aerobes: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophila*,

Other aerobes: *Mycoplasma pneumoniae, Chlamydia pneumoniae (TWAR)*

Mycobacteria: *Mycobacterium leprae, Mycobacterium kansasii, Mycobacterium chelonae,*

Mycobacterium fortuitum, Mycobacterium avium complex (MAC): Mycobacterium avium and Mycobacterium intracellulare

Beta lactamase production has no effect on clarithromycin activity.

NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Helicobacter: *Helicobacter pylori*

There is a strong link between *Helicobacter pylori* and peptic ulcer disease. Between 90% and 100% of patients with duodenal ulcers are infected with this pathogen. *H. pylori* eradication has been shown to reduce duodenal ulcer recurrence and therefore the need for continued antisecretory treatment.
Clarithromycin shows in vitro activity against most strains of the following microorganisms; however, the safety and efficacy of clarithromycin in the treatment of clinical infections caused by these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram positive aerobes: *Streptococcus agalactiae, Streptococci (Group C.F.G), Viridans group streptococci,*

Gram negative aerobes: *Bordetella pertussis, Pasteurella multocida,*

Gram positive anaerobes: *Clostridium perfringens, Peptococcus niger, Propionibacterium acnes*.

Gram negative anaerobes: *Bacteroides melaninogenicus*.

Spirochetes: *Borrelia burgdorferi, Treponema pallidum*

Campylobacter: *Campylobacter jejuni*

The major metabolite of clarithromycin is 14-OH clarithromycin, a metabolite with microbiological activity. This metabolite is as active as or 1-2 times less active than the parent compound for most organisms except *H. influenzae* , for which it is twice as active. The parent compound and 14 OH-metabolites exert additive or synergistic effects on *H. influenzae in vitro* and *in vivo*, depending on bacterial strains. However, the 14-OH metabolite is 4-7 times less effective than clarithromycin against *Mycobacterium avium* complex (MAC) isolates. The clinical significance of this activity against*Mycobacterium avium* complexes is unknown.

Susceptibility tests

Quantitative methods measuring zone diameters give the most accurate estimates of antibiotic susceptibility. A recommended procedure uses a disk impregnated with 15 mcg clarithromycin for susceptibility testing (Kirby-Bauer diffusion test); the inhibition zone diameters in this disk test correlate with clarithromycin MIC values. MIC values are determined by the broth or agar dilution method.

With this procedure, a "susceptible" statement in a report from the laboratory indicates that the infectious organism may respond to treatment. The term "resistant" in the report indicates that the organism causing the infection may not respond to treatment. The term "intermediate susceptibility" in the report suggests that the therapeutic effect of the drug may be uncertain or that the organism may be susceptible when high doses are used. (This last statement can also be specified as moderately susceptible).

Please refer to country- or region-specific information on absolute limits for susceptible, resistant and intermediate susceptibility.

5.2. Pharmacokinetic properties

General properties:

Pharmacokinetic studies on the concomitant administration of Clarithromycin 500 mg film coated tablet, Lansoprazole 30 mg micropellet capsule, Amoxicillin 1000 mg tablet have not been performed. No clinically significant drug interactions were observed when lansoprazole and amoxicillin or lansoprazole and clarithromycin were administered concomitantly. There are no data on gastric mucosal concentrations of clarithromycin, lansoprazole and amoxicillin

after concomitant administration of these three drugs. The following systematic pharmacokinetic information is based on studies in which each drug was administered alone.

Pharmacokinetic properties of clarithromycin

General characteristics
Clarithromycin is an antibiotic with antimicrobial action. Slightly soluble in ethanol, methanol and acetonitrile, insoluble in water.

Absorption:
Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of clarithromycin tablets is approximately 50%. Food intake immediately before the dose increases the bioavailability of clarithromycin by an average of 25%. Overall, this increase is minor and of little clinical significance at the recommended dosing regimens. Clarithromycin can therefore be taken on an empty or full stomach.

At a dose of 500 mg twice daily, the steady-state C_{max} for clarithromycin and its hydroxylated metabolite is reached by the fifth dose. After the fifth and seventh doses, mean steady-state C_{max} for clarithromycin was 2.7 to 2.9 mcg/mL and 0.88 to 0.83 mcg/mL for its hydroxylated metabolite. At the 500 mg dose level, the half-life is 4.5 to 4.8 hours for the parent drug and 6.9 to 8.7 hours for 14-hydroxyclarithromycin. Steady-state 14-hydroxyclarithromycin levels do not increase in proportion to clarithromycin dose, and the apparent half-lives of clarithromycin and its hydroxylated metabolite tend to be longer at higher doses.

Distribution:
Clarithromycin and its metabolite 14-OH clarithromycin are readily distributed into body tissues and fluids. Limited data from a small number of patients suggest that clarithromycin does not reach significant levels in cerebrospinal fluid after oral doses. Concentrations in tissues are several times higher than serum concentrations. Examples of tissue and serum concentrations are shown below.

CONCENTRATION (after a dose of 250 mg every 12 hours)		
Tissue Type	**Tissue (mcg/g)**	**Serum (mcg/mL)**
Tonsil	1.6	0.8
Lung	8.8	1.7

Biotransformation:
With a dose of 250 mg every 12 hours, the main metabolite 14-OH clarithromycin yields a steady-state peak concentration of approximately 0.6 mcg/mL and has an elimination half-life of 5-6 hours. With a dose of 500 mg every 12 hours, peak steady-state concentrations of 14-OH clarithromycin are slightly higher (up to 1mcg/mL) and the elimination half-life is approximately 7 hours. At both doses, steady-state concentrations of this metabolite are usually reached in 2-3 days.

Elimination:
In adult humans administered 250 mg or 1200 mg clarithromycin orally as a single dose, urinary excretion accounted for 37.9% of excretion at low doses and 46% at high doses. Fecal elimination was responsible for 40.2% and 29.1% of these doses, respectively (including one person with an excretion rate of 14.1% in a single stool sample).

Linearity/non-linearity:

This non-linear pharmacokinetic behavior of clarithromycin, together with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at higher doses, suggests that the non-linear metabolism of clarithromycin is more pronounced at higher doses.

Characteristics in patients

Hepatic impairment:

In a study comparing a healthy human group with a group with hepatic impairment, no significant difference was found between the groups in terms of steady-state plasma levels and systemic clearance of clarithromycin after administration of 250 mg clarithromycin twice daily and a single dose of 250 mg clarithromycin on the third day. In contrast, steady-state concentrations of the 14-OH metabolite were significantly lower in the group of subjects with hepatic impairment. This decrease in metabolic clearance of the parent compound via 14-hydroxylation is partially offset by an increase in renal clearance of the parent drug, resulting in comparable steady-state levels for the parent drug in healthy subjects and subjects with hepatic impairment. These results suggest that dose adjustment is not necessary in individuals with moderate or severe hepatic impairment but normal renal function.

Renal impairment:

In patients with renal impairment, plasma levels of clarithromycin and its 14-OH metabolite have higher half-life, C_{max} and C_{min}, and AUC is greater. Celim and urinary excretion are low. The degree of difference between these parameters is proportional to the degree of renal impairment; the more severe the renal impairment, the more significant the difference.

Elderly:

In the elderly, circulating plasma levels are higher and elimination slower for both the parent drug and the 14-OH metabolite. However, when renal clearance of clarithromycin was correlated with creatinine clearance, there was no difference between the two groups. Based on these results, it was concluded that clarithromycin-related effects were related to renal function and not to the age of the individual.

Mycobacterium avium infections

The steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following a 500 mg clarithromycin dose administered every 12 hours to adult patients with HIV infection were similar to those obtained in healthy volunteers. However, clarithromycin concentrations may be much higher at higher doses, which may be necessary to treat *Mycobacterium avium* infections. The steady-state clarithromycin C_{max} values in adult HIV-infected patients receiving 1000 and 2000 mg/day divided into two daily doses are between 2 and 4 mcg/mL and 5 and 10 mcg/mL, respectively. Elimination half-lives at these high doses appear to be prolonged compared to those seen at usual doses in normal individuals. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linear pharmacokinetics of clarithromycin.

Concomitant administration of omeprazole

When omeprazole was used with clarithromycin, the mean omeprazole AUC_{0-24} was 89% higher and the harmonic mean for omeprazole $T_{1/2}$ was 34% higher compared to omeprazole alone. When clarithromycin and omeprazole are administered concomitantly, the steady-state C_{max}, C_{min} and AUC_{0-8} values of clarithromycin increase by 10%, 27% and 15%, respectively, compared to the values obtained when clarithromycin is given with placebo.

At steady state, gastric mucosal clarithromycin concentrations were approximately 25-fold higher six hours post-dose in the clarithromycin/omeprazole group compared to the clarithromycin alone group.

6 hours after the dose, when clarithromycin was given together with omeprazole, the mean gastric tissue concentrations of clarithromycin were on average 2-fold higher than clarithromycin + placebo.

Pharmacokinetic properties of amoxicillin:

Absorption:

Amoxicillin is resistant to gastric acid and is rapidly absorbed after oral use. Approximately 1-2 hours after oral administration of 250 and 500 mg doses, blood concentrations range between 3.5 mcg/mL-5 mcg/mL and 5.5 mcg/mL-7.5 mcg/mL, respectively.

Distribution:

It is easily distributed to most of the body tissues and fluids. However, it can pass into the brain and cerebrospinal fluid when the meninges are inflamed. Amoxicillin has a low protein binding rate of approximately 20%.

Biotransformation:

Amoxicillin does not undergo significant metabolization.

Elimination:
Approximately 60% of orally administered amoxicillin is excreted unchanged in the urine within 6-8 hours. The half-life of amoxicillin is 61.3 minutes. Concomitant administration of probenecid with amoxicillin delays the excretion of amoxicillin.

Linearity/non-linearity:
Doubling the dose of amoxicillin results in approximately a two-fold increase in serum levels.

Pharmacokinetic properties of lansoprazole

Absorption:
Lansoprazole is administered as an enteric-coated formulation that enables intestinal absorption in order to prevent chemical changes in the stomach due to its acid-resistant chemical structure and to increase systemic bioavailability.

Absorption of orally administered lansoprazole in enteric-coated formulation is rapid, with maximum serum concentrations reached in approximately 1.7 hours. Lansoprazole does not accumulate in the body and its pharmacokinetic properties do not change when administered in repeated doses. Lansoprazole is rapidly absorbed, with C_{max} values reached 1.7 hours after oral administration and bioavailability of 80%. Absorption of lansoprazole is reduced in the presence of food in the stomach. Administration of the drug within 30 minutes after a meal, rather than on an empty stomach, led to a decrease in C_{max} and AUC of approximately 50%. The mean plasma half-life in healthy subjects is 1.5 (±1) hour.

Distribution:
Lansoprazole binds to protein at a rate of 97%. In the concentration range of 0.05-5 mcg/mL, the rate of binding to plasma proteins does not change.

Biotransformation:
Lansoprazole is highly metabolized in the liver; two metabolites (hydroxylated sulfinyl and sulfone) have been detected in measurable amounts in plasma. These metabolites have no or very low antisecretory activity. Although it is thought that lansoprazole is converted into two active metabolites that inhibit acid production via H+/K+ ATPase pathway in parietal cell canaliculi, these metabolites could not be demonstrated in blood. These metabolites are not found in the systemic circulation.

Elimination:
The elimination half-life of lansoprazole does not reflect how long it inhibits gastric acid secretion. The plasma elimination half-life is shorter than 2 hours, while the acid inhibitory effect lasts longer than 24 hours. Elimination half-life in the elderly is 2-3 hours.
Following oral administration of a single dose of lansoprazole, no unchanged drug was detected in the urine. In one study, following oral administration of a single dose of 14C, approximately 1/3 of the administered radiation was detected in urine and 2/3 in feces. This indicates that metabolites of lansoprazole are significantly excreted in bile.

Linearity/non-linearity:
The maximum serum concentrations (C_{max}) and area under the curve (AUC) values obtained with a single oral dose of 15-60 mg are directly proportional to the dose.

Characteristics in patients

Renal impairment:
In patients with severe renal impairment, binding to plasma proteins decreases by 1-1.5% after administration of 60 mg lansoprazole. In patients with renal impairment, the elimination half-life was shortened and the total AUC (free and protein-bound) was decreased. However, the AUC of free lansoprazole in plasma is not related to the degree of renal impairment. C_{max} and T_{max} values are similar to those in healthy people. No dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment:
In patients with varying degrees of hepatic impairment, the mean plasma half-life was prolonged from 1.5 hours to 3.2-7.2 hours. The mean AUC values of patients with hepatic impairment at steady state increased up to 500%. The dose of lansoprazole should be reduced in patients with severe hepatic impairment.

Geriatric patients:
In elderly patients, the clearance of lansoprazole is reduced and the elimination half-life is increased by 50-100%. Since the mean half-life in elderly patients is 1.9-2.9 hours, it has been found that it is not accumulated with repeated doses administered once a day. Peak plasma levels do not change in the elderly.

Pediatric population
Pharmacokinetic evaluation in children aged 1-17 years with a dose of 15 mg for children under 30 kg and 30 mg for children over 30 kg was similar to that in adults. Exposure to lansoprazole in children aged 2-3 months to 1 year at a dose of 17 mg/m^2 body surface area or 1 mg/kg was similar to that in adults. In infants younger than 2-3 months of age, higher exposure to lansoprazole was seen in adults with single doses of 1 mg/kg and 0.5 mg/kg.

Poor metabolizers of CYP2C19
CYP2C19 is the subject of genetic polymorphism, found in 2-6% of the population and referred to as poor metabolizers. The mutant is homozygous for a CYP2C19 allele and therefore the function of the CYP2C19 enzyme is deficient. Lansoprazole exposure is several times higher in poor metabolizers than in strong metabolizers.

5.3. Preclinical safety data
Lansoprazole:
Preclinical data based on traditional safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity studies have shown no harmful effects on humans.
In two carcinogenicity studies in rats, lansoprazole produced ECL cell carcinoids associated with dose-dependent gastric ECL cell hyperplasia and hypergastrinemia due to inhibition of acid secretion. Leydig cell hyperplasia, benign Leydig cell tumors and intestinal metaplasia were also observed. Retinal atrophy occurred after eighteen months of treatment. This has not been seen in monkeys, dogs and mice. The clinical relevance of these findings is unknown.

Amoxicillin
Long-term studies were not conducted to evaluate the carcinogenic potential of amoxicillin. Mutagenic potential of amoxicillin alone has also not been evaluated. Information is available from tests with amoxicillin clavulanate. Amoxicillin clavulanate did not show mutagenicity in the bacterial mutation method and yeast gene conversion method. It was found weakly positive in the mouse lymphoma method. However, increased mutation frequencies in this method are associated with reduced cell survival. Amoxicillin clavulanate was found to be negative in the mouse micronucleus test and the dominant lethal method in mice. Potassium clavulanate alone was evaluated in the Ames bacterial mutation method and in the mouse micronucleus assay and negative results were obtained in both methods. In multi-generation reproduction studies in rats, no human fertility impairment or other reproductive side effects were observed at doses up to 500 mg/kg (approximately 3 times the human dose per mg/m^2).

Clarithromycin
Acute, Subchronic and Chronic Toxicity: Studies have been conducted in mice, rats, dogs and/or monkeys administered clarithromycin orally. The duration of administration ranged

from a single oral dose to repeated daily doses over 6 consecutive months. In acute mouse and rat studies, following a single gavage at 5 g/kg body weight, 1 rat died and no mice died. Thus, the median lethal dose is greater than 5 g/kg (the highest feasible dose for administration).
Primates exposed to clarithromycin at a dose of 100 mg/kg/day for 14 days or 35 mg/kg/day for 1 month showed no adverse effects attributable to clarithromycin. Similarly, no adverse effects were observed in rats exposed to 75 mg/kg/day for 1 month, 35 mg/kg/day for 3 months or 8 mg/kg/day for 6 months. Dogs that tolerated 50 mg/kg/day for 14 days, 10 mg/kg/day for 1 and 3 months and 4 mg/kg/day for 6 months without adverse effects were more sensitive to clarithromycin.
In these aforementioned clinical trials, important clinical signs at toxic doses include vomiting, weakness, decreased food consumption and weight gain, salivation, dehydration and hyperactivity. Two of the 10 monkeys administered the 400 mg/kg/day dose died on treatment day 8; some living monkeys administered clarithromycin 400 mg/kg/day for 28 days had yellow feces in some isolated cases.
At toxic doses in all species, the primary target organ was the liver. The development of hepatotoxicity in all species was detectable by early increases in serum concentrations of alkaline phosphatase, alanine and aspartate amino transferase, gammaglutamyl transferase and/or lactic dehydrogenase. Discontinuation of the drug resulted in the normalization of the concentrations of these specific parameters.
Organs less affected in various studies are the stomach, thymus and other lymphatic tissues and kidneys. Following near-therapeutic doses, conjunctival infection and lacrimation were seen only in dogs. At an intensive dose of 400 mg/kg/day, corneal opacity and/or edema was observed in some dogs and monkeys.

Fertility, Reproduction and Teratogenicity: In fertility and reproduction studies, doses of 150-160 mg/kg/day did not cause any adverse effects on the estrous cycle, fertility, parturition, number and survival of male and female rats.
Two teratogenicity studies in Wistar (po) and Spraque-Dawley (po and IV) rats, a study in New Zealand rabbits and a study in cynomolgus monkeys showed no teratogenicity from clarithromycin. Only in an additional study in Sprague-Dawley rats at similar doses and under similar conditions cardiovascular abnormalities occurred at a statistically insignificant incidence (approximately 6%). These anomalies appear to be due to the spontaneous expression of genetic changes within the colony. In two studies in rats, congenital cleft palate was observed with variable incidence (from 3% to 30%) following administration of a dose 70 times the upper limit of the daily clinical dose used in humans (500 mg BID); the absence of this anomaly at 35 times the daily clinical dose suggests maternal and fetal toxicity, but not teratogenicity.

Clarithromycin administered at approximately 10 times the upper limit of the human daily dose (500 mg BID) caused embryonic loss (abortion) in monkeys from day 20 of gestation. This effect has been attributed to the maternal toxicity of the drug at very, very high doses. In an additional study in pregnant monkeys administered approximately 2.5-5 times the maximum daily dose, there was no fetal harm.
The dominant lethal test in mice at a dose of 1000 mg/kg/day (approximately 70 times the maximum human daily clinical dose) was clearly negative for mutagenic activity; and in a segment 1 study in rats administered doses of up to 500 mg/kg/day for 80 days (approximately 35 times the maximum daily human clinical dose), no functional impairment of male fertility was found due to such prolonged exposure to these very high doses of clarithromycin.

Mutagenicity: Studies were conducted to evaluate the mutagenic potential of clarithromycin using both unactivated and rat-liver-microsome activated test systems (Ames Test). These studies found no evidence of mutagenic potential at drug concentrations of 25 mcg/petri or less. At a concentration of 50 mcg the drug is toxic to all strains tested.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Clarithromycin 500 mg Film Coated Tablets

Croscarmellose sodium
Microcrystalline cellulose PH 101
Microcrystalline cellulose PH 102
Polyvinylpyrrolidone K25
Colloidal silicon dioxide
Magnesium stearate
Talc
Film coating agent: Opadry 03B22320 yellow
Hydroxypropylmethylcellulose
Titanium dioxide
Polyethylene glycol
Indigo Carmine
Tartrazine

Lansoprazole 30 mg Micropellet Capsules

Sodium lauryl sulfate
Methyl hydroxypropylcellulose
Talc
Titanium dioxide
Ployethylene Glycol 6000
Polysorbate 80
Polyacrylate
Sucrose
Maize starch
N-Methyl glucamine
Mannitol
Gelatin (from bovine bone)
Quinoline Yellow
Erythrosine FD&C Red 3
Iron oxide yellow

Amoxicillin 1000 mg Tablet

Crospovidone
Mint flavor
Sodium cyclamate
Saccharin sodium
Magnesium stearate

6.2. Incompatibilities

TRIO does not have any incompatibility.

6.3. Shelf life
36 months.

6.4. Special precautions for storage
Store it at room temperature below 25°C, in its original box. Protect from light and moisture.

6.5. Nature and contents of container
One side in transparent PVC/Aclar, the other side in printed aluminum foil.
- 2 × Clarithromycin 500 mg Film Coated Tablets
- 2 × Lansoprazole 30 mg Micropellet Capsules
- 2 × Blisters containing Amoxicillin 1000 mg Tablets

Each cardboard box contains 7 or 14 blisters.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)
206/11

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of first authorization : 01.07.2005
Renewal of the authorization :

10. DATE OF REVISION OF THE TEXT