INSTRUCTION FOR THE MEDICAL USE
CLARITHROMYCIN-TF
lyophilized powder
for solution for infusion 500 mg

Trade name Clarithromycin-TF.
International nonproprietary name Clarithromycin.
Pharmaceutical form Lyophilized powder for solution for infusion 500 mg.
Description White to off-white lyophilized powder.
1 vial contains:
Active ingredient:
clarithromycin – 500 mg;
Excipients: lactobionic acid, 1 M sodium hydroxide solution.
Pharmacotherapeutic group: Antibacterials for systemic use. Macrolides.
ATC code J01FA09.
Pharmacological properties:
Pharmacodynamics
The active ingredient of Clarithromycin-TF is clarithromycin. Clarithromycin is a semisynthetic macrolide antibiotic derived by substitution of CH_3O hydroxyl group by (OH) group in the 6^{th} position of the lactone ring of erythromycin, more precisely, clarithromycin is 6-O-methylerythromycin A. The mechanism of action of clarithromycin is based on binding to 50S ribosomal subunit of sensitive bacteria, which prevents the translocation of activated amino acids. Clarithromycin inhibits intracellular protein synthesis of microorganisms sensitive thereto and thereby exerts its antibacterial action.
Clarithromycin demonstrated high efficacy *in vitro* against standard laboratory strains of clinical isolates. It shows high efficiency against many aerobic and anaerobic gram-positive and gram-negative microorganisms. The minimum inhibitory concentrations (MICs) of clarithromycin for most pathogens are generally two-fold lower than the MICs of erythromycin.
The 14-(R)-hydroxy metabolite of clarithromycin exhibits antimicrobial activity. For most microorganisms activity of this metabolite is equal, or 2-fold higher than the starting compound, and the MICs of metabolite are twice higher the MIC of clarithromycin in relation to *Haemophilus influenzae*.
The *in vitro* data show a high efficiency of clarithromycin against gram-positive microorganisms: *Staphylococcus aureus* (methicillin-susceptible), *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), alpha hemolytic streptococci (viridans group), *Streptococcus pneumoniae, Streptococcus agalactiae, Listeria monocytogenes*; gram-negative microorganisms: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophila, Bordetella pertussis, Helicobacter pylori, Campylobacter jejuni*; mycoplasma: *Mycoplasma pneumoniae, Ureaplasma urealyticum*; anaerobes: *Bacteroides fragilis (macrolide-susceptible strains), Clostridium perfringens, Peptococcus species, Peptostreptococcus species, Propionibacterium acnes*; other microorganisms: *Chlamydia trachomatis, Mycobacterium avium, Mycobacterium leprae, Chlamydia pneumoniae*.
Clarithromycin has bactericidal properties against *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella catarrhalis, Neisseria gonorrhoeae, Helicobacter pylori* (the activity is higher at neutral pH), and *Campylobacter spp*.

Pharmacokinetics

In a clinical study with healthy volunteers, clarithromycin was administered IV as a single dose of 75 mg, 125 mg, 250 mg or 500 mg in a volume of 100 ml as an infusion for 30 minutes; and at doses of 500 mg, 750 mg or 1000 mg in a volume of 250 ml as an infusion over 60 minutes. Mean maximum concentrations (C_{max}) of clarithromycin ranged from 1.23 μg/ml and 9.40 μg/ml after infusions of 75 mg and 1000 mg of clarithromycin, respectively. The mean maximum concentrations (C_{max}) of 14-(R)-hydroxy metabolite were 0.21 μg/ml after infusions of 125 mg and 1.06 μg/ml after administration of 1000 mg of clarithromycin. No metabolite was found at a dose less than 75 mg.

The half-life of clarithromycin depended on dose and was 2.1-4.5 hours after administration of 75 mg and 1000 mg. The average half-life in blood plasma for 14-(R)-hydroxy metabolite ranged from 5.3 to 9.3 hours after administration of 250 mg and 1000 mg, respectively.

The average half-life after a 30-minute infusion of 125 mg of clarithromycin was 7.2 hours. The average value of the area under the curve "concentration-time" (AUC) of clarithromycin showed nonlinear dose-dependent increase from 2.29 h·μg/ml after administration of 75 mg to 53.26 μg·h/ml after administration of 1000 mg. The mean value of AUC 14-(R)-hydroxy metabolite was from 2.10 h·μg/ml to 14.76 h·μg/ml if administered at doses of 125 mg and 1000 mg, respectively.

In 7-day clinical study, clarithromycin was repeatedly injected intravenously at doses of 125 mg and 250 mg in a volume of 100 ml for more than 30 minutes and at doses of 500 mg and 750 mg in a volume of 250 ml for more than 60 minutes every 12 hours. In this study, C_{max} value increased from 2.1 μg/ml upon administration of 125 mg to 3.2 μg/ml, 5.5 μg/ml, 8.6 μg/ml when administered 250 mg, 500 mg and 750 mg, respectively. The half-life was increased gradually from 2.8 hours after administration of 125 mg to 6.3 hours after administration of 500 mg. When administered 750 mg, the half-life was 4.8 hours.

C_{max} of 14-(R)-hydroxy metabolite at steady state increased from 0.33 μg/ml after administration of 125 mg to 0.55 μg/ml, 1.02 μg/ml and 1.37 μg/ml after administration of 250 mg, 500 mg and 750 mg, respectively. The half-life for the metabolite was 4.8, 5.4, 7.9 and 5.4 hours after administration of 125 mg, 250 mg, 500 mg and 750 mg, respectively. Pharmacokinetics of 14-(R)-hydroxy metabolite was dose-independent.

Protein binding

Clarithromycin binding to plasma proteins depends on the concentration and varies from 72% to 67% and its active metabolite - from 57% to 48%.

Tissue distribution

The volume of distribution is about 2-4 L/kg. After administration of five doses of 250 mg, the concentrations of 8.8 μg/ml, 1.11 μg/ml and 0.9 μg/ml were found in the lungs, tonsils and in the interstitial fluid, respectively. Macrolides penetrate and accumulate in phagocytes (polynuclear neutrophils, monocytes, peritoneal and alveolar macrophages). In humans, high levels can be detected inside the phagocytes. Such properties explain the activity of clarithromycin in relation to intracellular bacteria. Clarithromycin and 14-(R)-hydroxy metabolite can be excreted into the breast milk. Concentration in breast milk and plasma concentration is 24% and 63%, respectively.

Biotransformation

Clarithromycin is converted into three metabolites: decladinosyl-clarithromycin, N-dimethyl clarithromycin and 14-(R)-hydroxy-clarithromycin. The latter metabolite is the predominant metabolite quantitatively and qualitatively, as it has its antibacterial activity. 14-(R)-hydroxy-clarithromycin is formed by first pass metabolism, as indicated by lower bioavailability of the metabolite following intravenous administration. In the administration of higher doses of

clarithromycin the metabolism is saturated. The increase in dosage and in the number of administrations may result in increased plasma concentrations of clarithromycin that are proportionally higher than those observed after a single dose administration and decrease in the proportion of 14-(R)-hydroxy metabolite (at steady state the plasma levels of 14-(R)-hydroxy metabolite are approximately 2/3 of the starting compound after a double administration of 250 mg and about 27% after the double administration of 500 mg).

Elimination

Clarithromycin is eliminated in the liver and kidneys. In humans, after a single oral administration of 250 mg, 37.9% of the dose are excreted in the urine, of which 18.4% of clarithromycin and 13.7% of 14-(R)-hydroxy-clarithromycin. Free clarithromycin and 14-(R)-hydroxy-clarithromycin are a major part of the urinary excretion of clarithromycin regardless of the dose.

The elimination in the faeces of a single dose of 250 mg was 40.2%, of which 4.4% - the starter compound. The main part of clarithromycin dose is excreted as metabolites. Increasing doses leads to increased urinary excretion and the proportion of unchanged clarithromycin.

Pharmacokinetics in special clinical situations

In patients with *renal insufficiency* the levels of clarithromycin and especially 14-(R)-hydroxy-clarithromycin excretion are decreased, resulting in increase of maximum concentration, residual concentrations, increase of area under the AUC curve and increase in concentrations of 14-(R)-hydroxy metabolite. In patients with clearance less than 30 ml/min, half-life is increased by 3 times and 4 times for 14-(R)-hydroxy-clarithromycin with a significant risk of accumulation.

In patients with *hepatic insufficiency* the formation of 14-(R)-hydroxy-clarithromycin was decreased, its serum concentrations and AUC decreased accordingly. However, reducing the formation of 14-(R)-hydroxy metabolite was offset by the increase in excretion the clarithromycin through the kidneys, no accumulation were found.

In *elderly patients* (> 65 years old), C_{max} and residual concentrations increased, which was associated with a longer half-life of clarithromycin (> 7.7 hours), and especially 14-(R)-hydroxy metabolite (14 hours). The AUC areas of clarithromycin were 2-fold higher than in the group of young people.

Therapeutic indications

Clarithromycin-TF is indicated in adults and children 12 years and older whenever parenteral therapy is required for treatment of infections caused by clarithromycin-susceptible microorganisms:

- lower respiratory tract infections: acute or chronic bronchitis, pneumonia;
- upper respiratory tract infections, such as sinusitis or pharyngitis;
- skin and soft tissue infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Contraindications

Clarithromycin is contradicted in patients with known hypersensitivity to macrolide antibiotics or any of its excipients contained in the drug product.

Concomitant use of clarithromycin with the following medicines is contradicted: astemizole, mizolastine, terfenadine, cisapride, pimozide, ivabradine, bepridil, dronedarone, sertindole (as it may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and torsade de pointes).

The concomitant use of clarithromycin with ergot alkaloids (e.g., ergotamine, dihydroergotamine, methylergometrine, methysergide) is contradicted as it can result in ergot toxicity).

The concomitant use of clarithromycin with midazolam for the oral administration.

Clarithromycin-TF should not be used in patients with QT prolongation or the history of ventricular cardiac arrhythmia, including torsade de pointes. The use of clarithromycin in patients with hypokalemia (risk of QT prolongation).
Clarithromycin-TF should not be used in patients with severe hepatic insufficiency in combination with renal insufficiency.
The concomitant use of clarithromycin with HMG-CoA reductase inhibitors (statins), which are extensively metabolized by CYP3A4 isoenzyme (lovastatin or simvastatin), due to the risk of myopathy, including rhabdomyolysis.
The concomitant use of clarithromycin (as well as other strong CYP3A4 inhibitors) with colchicine, ticagrelor and ranolazine is contraindicated.
The concomitant use of quetiapine and clarithromycin is contraindicated due to risk of a significant increase level of quetiapine and, as a consequence, overdose.

Precautions for use

Pregnancy and lactation

Clinical safety of clarithromycin *during pregnancy* has not been established. Clarithromycin-TF should not be administered to pregnant women, especially in the first three months of pregnancy, except cases when the potential benefits of treatment outweigh any potential risk to the fetus. In each case, the drug must be used under the direct supervision of a physician.
The safety of clarithromycin *during lactation* has not been established. Clarithromycin may be excreted into breast milk. If necessary to use the Clarithromycin-TF during lactation, the termination of breastfeeding should be considered.

Special warnings

The prolonged use of Clarithromycin-TF, as in case with other antibiotics, may cause excessive growth of insensitive bacteria and fungi. The appropriate therapy should be started in the event of super infection.
The *precautions* should be observed when administering the drug in patients with severe renal insufficiency.
Clarithromycin is mainly eliminated by liver. Therefore cautions should be exercise when using the drug in patients with *impaired hepatic function*.
Cases of hepatic failure have been reported, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis with jaundice or without it. Liver dysfunction may be severe and is usually reversible. Fatal cases of hepatic failure were mainly associated with serious underlying diseases and/or concomitant medication treatment. It is necessary to stop immediately the use of clarithromycin if signs or symptoms of hepatitis as anorexia, jaundice, dark urine, itching, or abdominal pain develop.
When using nearly all antibacterial agents, including macrolides, there is the possibility of pseudomembranous colitis, which severity can range from mild to life-threatening. There is also a risk of diarrhea associated with *Clostridium difficile* (CDAD), and its severity can range from mild diarrhea to fatal colitis. The treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD should be considered in all patients with diarrhea following antibiotic use. Careful history is necessary since CDAD has been reported to occur over two months after receiving antibacterial agents.
The colchicine toxicity (including fatal) has been reported with concomitant use of clarithromycin and colchicine, especially in elderly, including patients with renal insufficiency.
The concomitant use of clarithromycin and colchicine is contraindicated.
The caution should be exercised when administering clarithromycin concomitantly with triazolobenzodiazepines, such as triazolam, intravenous midazolam.

Clarithromycin should be used with caution if administered concomitantly with other ototoxic drugs such as aminoglycosides. During and after treatment the monitoring of hearing and vestibular function is recommended.

Cardiovascular adverse events

Prolonged cardiac repolarization and QT interval imparing a risk of cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides, including clarithromycin. Since the following conditions may increase the risk of developing ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution:

- in patients with coronary artery disease, severe cardiac insufficiency, conduction disorders and clinically significant bradycardia;
- in patients with an electrolyte disturbance, such as hypomagnesemia. Clarithromycin must not be given to patients with hypokalemia;
- concomitantly with other drug products with established risk of QT prolongation;
- concomitantly with *astemizole, cisapride, pimozide, terfenadine* is contraindicated.
- clarithromycin must not be used in patients with congenital or acquired QT prolongation or ventricular arrhythmia in a history.

Epidemiological studies to assess the risk of cardiovascular adverse outcomes have shown variable results. In some observational studies, the risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with the use of macrolides, including clarithromycin, has been reported. When prescribing clarithromycin, it is necessary to take into account the information received and benefits of treatment.

In view of the increasing resistance of *Streptococcus pneumoniae* to macrolides, a sensitivity test should be performed when administering Clarithromycin-TF for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with other appropriate antibiotics.

Infections of the skin and soft tissues of mild to moderate severity are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. In cases where beta-lactam antibiotics cannot be used, other antibiotics, such as clindamycin, may be used as first choice medicine. Currently, macrolides play a role only in the treatment of certain infections of the skin and soft tissues: infections caused by *Corynebacterium minutissimum, Acne vulgaris*; erysipelatous inflammation; and in situations where penicillin treatment cannot be administered.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe skin reactions (e.g., acute generalized exanthematous pustulosis (AGEP)), Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS-syndrome, Clarithromycin-TF therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin-TF should be used with caution in concomitant administration with inducers of cytochrome CYP3A4 enzyme.

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

The concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. Clarithromycin should be used with caution concomitantly with other statins, as it was reported on the development of rhabdomyolysis in case of concomitant use. Signs and symptoms of myopathy should be monitored. In situations where simultaneous use of clarithromycin with statins cannot be avoided, it is recommended to administer the lowest registered dose of the statin. The use of statin not metabolized by CYP3A (e.g., fluvastatin) is possible.

Co-administration of clarithromycin and oral hypoglycemic agents (such as sulfonylurea) and/or insulin can cause severe hypoglycemia. Careful monitoring of blood glucose is recommended.

In concomitant use of clarithromycin and warfarin there is a risk of serious hemorrhage, and significant elevations in INR (international normalized ratio) indicator and prothrombin time. In patients taking both clarithromycin and oral anticoagulants, the INR and prothrombin time should be monitored frequently.

Effects on ability to drive and use machines are currently not known. It is necessary to take into account the possibility of seizures, dizziness, vertigo, hallucinations, confusion, disorientation, etc., which could affect the speed of psychomotor reactions.

Posology and method of administration

For intravenous administration only. The duration of intravenous therapy may be limited to 2-5 days, depending on the severity of the infection and condition of the patient, and should be changed to oral clarithromycin therapy whenever possible.

The recommended dosage of clarithromycin for *adults and adolescents over 12 years old* is 1 g daily divided into two 500 mg doses which are administered within 60 minutes after dissolution with a suitable solvent to one of the large proximal veins using a solution concentration of 2 mg/ml.

Clarithromycin-TF should not be used for bolus or intramuscular administration!

In patients with *renal impairment* with creatinine clearance less than 30 ml/min, the clarithromycin dose should be reduced by one half of the usual recommended dose.

The intravenous administration of the drug in *children younger than 12 years* is not recommended.

Elderly patients: dosage adjustment is not required.

Preparation of solution

The solution is prepared immediately before drug administration. To prepare Clarithromycin-TF solution with a concentration of 2 mg/ml, add 10 ml of sterile water for injection into vial with the drug. *Use only sterile water for injection, as other solvents may cause precipitation*. Do not use diluents containing inorganic salts or preservatives.

The resultant solution should be added to a minimum of 250 ml of the following diluents before administration: isotonic saline, 5% glucose solution, lactated Ringer's solution.

Adverse events

When using Clarithromycin-TF, the adverse events listed below can be reported. When specifying the frequency, the following categories are used: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥1/10 000, <1/1000), very rare (<1/10000); unknown (cannot be estimated from the available data).

Infections and infestations: uncommon: cellulitis, candidosis, vaginal infection; unknown: pseudomembranous colitis, erysipelas.

Blood and lymphatic system disorders: uncommon: leukopenia; unknown: agranulocytosis, thrombocytopenia.

Immune system disorders: uncommon: anaphylactoid reaction, hypersensitivity; unknown: anaphylactic reaction, angioedema.

Metabolism and nutrition disorders: rare: anorexia, decreased appetite.

Mental disorders: common: insomnia; uncommon: anxiety; unknown: psychotic disorders, confusion, depression, disorientation, hallucinations, nightmares, mania.

Ear and labyrinth disorders: uncommon: vestibular vertigo, hearing disorder, tinnitus; unknown: deafness.

Nervous system disorders: common: dysgeusia, headache, taste perversion; uncommon: loss of consciousness, dyskinesia, dizziness, somnolence, tremor; unknown: convulsions, ageusia, parosmiya, anosmia, paresthesia.

Cardiac system disorders: uncommon: cardiac arrest, atrial fibrillation, QT prolongation, extrasystole, palpitations; unknown: torsade de pointes, ventricular tachycardia.
Vascular system disorders: common: vasodilatation; unknown: hemorrhage.
Respiratory, thoracic and mediastinal disorders: uncommon: asthma, nasal hemorrhage, pulmonary embolism.
Gastrointestinal disorders: common: diarrhea, vomiting, dyspepsia, nausea, abdominal pain; uncommon: oesophagitis, gastritis, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence; unknown: acute pancreatitis, tongue discoloration, teeth discoloration.
Hepatobiliary disorders: common: abnormal liver function tests; uncommon: increased levels of alanine aminotransferase, increased aspartate aminotransferase; unknown: liver failure, hepatocellular jaundice.
Skin and subcutaneous tissue disorders: common: rash, hyperhidrosis; uncommon: bullous dermatitis, pruritus, urticaria; unknown: acute generalised exanthematous pustulosis (AGEP). Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, acne.
Musculoskeletal and connective tissue disorders: uncommon: musculoskeletal stiffness; unknown: myopathy.
Renal and urinary disorders: uncommon: increased blood creatinine levels, increased blood urea; unknown: renal failure, interstitial nephritis.
General disorders and administration site conditions: very common: phlebitis at the injection site; common: pain at the injection site, inflammation at the injection site; uncommon: asthenia.
Investigations: uncommon: change in the ratio of albumin-globulin; unknown: increased INR values, increased prothrombin time, urine color changes.
Patients with impaired immune systems
In AIDS patients and other patients with impaired immune systems used higher doses of clarithromycin over long periods of time for the treatment of mycobacterial infections, it is not always possible to distinguish between adverse reactions associated with the use of the drug, and symptoms of HIV infection or associated diseases.
In adult patients who received clarithromycin in a daily dose of 1000 mg, the most common adverse events were nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatalence, headache, constipation, hearing impairment, increased ALT and AST levels. Dyspnea, insomnia, and dry mouth were reported sometimes. The laboratory parameters were evaluated in immunocompromised patients by analyzing their significant deviations from the standard values (i.e., a sharp increase or decrease). On the basis of these criteria, 2-3% of patients treated with clarithromycin 1000 mg daily demonstrated a significant increase in AST levels and ALT levels, and abnormally low white cells and platelet numbers. Several patients showed elevated blood urea nitrogen levels.
Adverse reactions reporting
It is important to report suspected adverse reactions after authorization of the medical product to ensure continuous monitoring of the drug benefit/ risk ratio. Healthcare professionals are asked to report any suspected adverse reactions and inefficiencies via national adverse drug reactions reporting system.
If the patient develops any adverse reaction, it is recommended to consult a physician. This recommendation applies to any possible adverse reactions, including those not listed in the instructions for use of the drug product. You can also report adverse reactions to the information database on adverse reactions (actions) to drug products, including reports of drug inefficiencies. Reporting adverse reactions, you help to get more information about the safety of the drug.

Overdose

No information on clarithromycin overdosing is available when administered intravenously. *Symptoms:* intake of a large dose of clarithromycin may cause symptoms of gastrointestinal disorders. Altered mental status, paranoid behavior, hypokalemia and hypoxemia were reported in one patient with the history of bipolar disorder ingested 8 g of clarithromycin.

Treatment: as with other macrolides hemodialysis and peritoneal dialysis have no significant effect on clarithromycin serum levels. In the case of overdose, the treatment with Clarithromycin-TF must be withdrawn and the symptomatic therapy should be administered.

Interaction with other medical products

Drug products the concomitant use of which is contraindicated

Cisapride, pimozide, astemizole and terfenadine. Increased levels of cisapride, pimozide, mizolastine, terfenadine, dronedarone, bepridil, ivabradine, sertindole in the serum was observed when used together with clarithromycin, which 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 astemizole and other macrolides concomitantly.

Ergot alkaloids. Concomitant use of clarithromycin and derivatives of ergot alkaloids (ergotamine, dihydroergotamine, methylergometrine, methysergide) was associated with symptoms of acute ergotism, which was characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated.

HMG-CoA reductase inhibitors. The concomitant use of clarithromycin and HMG-CoA reductase inhibitors (statins) (lovastatin or simvastatin) is contraindicated since these statins are largely metabolized by CYP3A4 and concomitant use of clarithromycin increases their concentration in the blood plasma, which in turn increases the risk of myopathy, including rhabdomyolysis. If treatment with clarithromycin cannot be avoided therapy with lovastatin or simvastatin should be discontinued during the treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statins. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. Signs and symptoms of myopathy should be monitored.

The concomitant use of clarithromycin increases the serum concentration of ticagrelor due to the decrease of its metabolism in liver and reduction of the concentration of the active metabolite.

Oral midazolam

In the concomitant use of midazolam and clarithromycin tablets (500 mg twice daily), midazolam AUC increased 7-fold after oral administration of midazolam. Simultaneous administration of oral midazolam and clarithromycin is contraindicated (see section "Contraindications").

Quetiapine

Significant increase in quetiapine concentration with a risk of overdose.

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. In the combined use of clarithromycin and colchicine, inhibition of Pgp and/or CYP3A may lead to increased colchicine exposure. Concomitant use of clarithromycin and colchicine is contraindicated.

Effect of other drugs on clarithromycin

CYP3A inducers. Drugs that are CYP3A inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort), may induce metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin and reduce its efficacy. Furthermore, it might require monitoring of plasma levels of CYP3A inducer, which could be increased due to the inhibition of CYP3A by clarithromycin. Concomitant use of rifabutin and clarithromycin resulted in increased levels of rifabutin and decrease of clarithromycin serum levels together with the increased risk of uveitis.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine. Strong inducers of cytochrome P450 enzymes such as efavirenz, nevirapine, rifampicin, rifapentine and rifabutin, may accelerate the metabolism of clarithromycin, reducing its plasma levels while increasing the concentration of 14-(OH)-(R)-clarithromycin - microbiologically active metabolite. Since the microbiological activity of clarithromycin and 14-(OH)-(R)-clarithromycin varies with respect to various bacteria, the expected therapeutic effect may be lowered due to the concomitant use of clarithromycin and enzyme inducers.

Etravirine. Etravirine can reduce the effect of clarithromycin; however, the concentration of the active metabolite 14-(R)-hydroxy-clarithromycin was increased. As the 14-(R)-hydroxy metabolite has a reduced activity against *Mycobacterium avium complex (MAC)*, overall activity against this pathogen can be changed. Therefore, the use of medicines alternative to clarithromycin should be considered for the treatment of MAC.

Fluconazole. The concomitant administration of fluconazole at a dose of 200 mg daily and clarithromycin 500 mg twice a day in 21 healthy volunteer resulted in an increase in average minimum equilibrium concentration of clarithromycin (C_{min}) and the area under the curve (AUC) of 33% and 18%, respectively. The equilibrium concentrations of the active metabolite 14-(R)-hydroxy-clarithromycin were not significantly changed when combined with fluconazole. Changing the dosage of clarithromycin is not required.

Ritonavir. A pharmacokinetic study demonstrated that co-administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours led to a marked inhibition of the metabolism of clarithromycin. Co-administration of ritonavir increased C_{max} of clarithromycin by 31%, C_{min} – by 182% and AUC – by 77%. The complete inhibition of the formation of 14-(R)-hydroxy-clarithromycin was reported. Because of the wide range of therapeutic dose for clarithromycin no dosage should be necessary in patients with normal renal function. However, the patients with renal impairment require dose adjustments: for patients with creatinine clearance 30 to 60 ml/min the dose of clarithromycin should be decreased by 50%, for patients with creatinine clearance <30 ml/min – by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when using ritonavir as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir.

Effect of clarithromycin on other medicinal products

CYP3A-based interactions. The co-administration of clarithromycin known to inhibit of the CYP3A, and a drug primarily metabolized CYP3A, may lead to increased drug concentrations in plasma, which could enhance or prolong its therapeutic effect and the risk of adverse reactions.

Caution should be observed when administering clarithromycin in patients receiving treatment with other drugs known to be CYP3A substrates, especially if CYP3A-substrate has a narrow therapeutic range (e.g., carbamazepine) and/or extensively metabolized by this enzyme.

Dosage adjustments may be required and, when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drugs classes are known or suspected to be metabolized by the same CYP3A isoenzyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g., warfarin), a typical antipsychotics (e.g., quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, sirolimus, terfenadine, triazolam and vinblastine, but this list is not exhausted. Similar mechanism of interaction was observed with the use of phenytoin, theophylline and valproate, that are metabolized by other isoenzyme of cytochrome P450 system.

Antiarrhythmics. There have been post-marketing reports of the torsade de pointes occurring with the concomitant use of clarithromycin and quinidine or disopyramide. The ECG monitoring is recommended for early detection of QT prolongation. During clarithromycin therapy serum levels of these drugs should be monitored.

There have been post-marketing reports of hypoglycemia in concomitant use of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant use of clarithromycin and disopyramide.

Oral hypoglycemic agents/insulin. In concomitant use with some hypoglycemic agents such as repaglinide and nateglinide, clarithromycin can inhibit CYP3A that can cause hypoglycemia. Careful glucose monitoring is recommended.

Omeprazole. Clarithromycin (500 mg every 8 hours) was given with omeprazole (40 mg daily) to healthy adult subjects. In concomitant use of clarithromycin and omeprazole, the equilibrium plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24} and $T_{1/2}$ increased by 30%, 89% and 34%, respectively). The mean gastric pH value was 5.2 during the administration of omeprazole only and 5.7 during the co-administration of omeprazole with clarithromycin.

Ranitidine bismuth citrate. The concomitant use of clarithromycin and ranitidine bismuth citrate resulted in increased plasma concentrations of ranitidine (57%), bismuth (48%) and 14-(R)-hydroxy clarithromycin (31%); these effects were not clinically significant.

Sildenafil, tadalafil, vardenafil. Phosphodiesterase inhibitors are metabolized (at least partially) with CYP3A and CYP3A can be inhibited by concomitant clarithromycin administrated. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil may result in increased phosphodiesterase inhibitor exposure. When using these medicines together with clarithromycin, the dose reduction of sildenafil, tadalafil, or vardenafil should be considered.

Theophylline, carbamazepine. Clinical studies have shown that there was a modest, but statistically significant increase of circulating theophylline or carbamazepine levels in concomitant use with clarithromycin. Plasma concentrations should be carefully monitored. Dose adjustment may be required.

Triazolobenzodiazepines. In concomitant use of midazolam with clarithromycin tablets (500 mg twice daily) AUC of midazolam increased 2.7-fold after intravenous administration of midazolam. In case of intravenous use of midazolam with clarithromycin, the patient should be closely monitored for timely dose adjustment. The concomitant use of oral midazolam and clarithromycin should be avoided. It should observe the same precautions when using other CYP3A-metabolized benzodiazepines, including triazolam and alprazolam. For benzodiazepines, the elimination of which is not dependent on CYP3A (temazepam, nitrazepam, lorazepam), a clinically significant interaction with clarithromycin is unlikely.

Triazolam. The drug interactions and adverse events in the central nervous system (e.g. somnolence and confusion) with the combined use of clarithromycin and triazolam have been

reported. It is necessary to monitor the patient, taking into account the possibility of intensification of the pharmacological effects on the CNS.

Medicinal products the combined use of which is not recommended

Bromocriptine, cabergoline, lisuride, pergolide. Derivatives of ergot alkaloids with dopaminergic activity (bromocriptine, cabergoline, lisuride, pergolide). In concomitant use with clarithromycin, the increase of plasma levels of dopamine with the risk of overdose is possible.

Alfuzosin, disopyramide. There is a risk of increased plasma levels of alfuzosin and manifestation of its adverse events. There is also a high risk of adverse events of disopyramide: severe hypoglycemia, QT prolongation, serious ventricular arrhythmias, including torsade de pointes.

There is an increased risk of ventricular arrhythmias in patients with congenital syndrome of QT prolongation.

Fesoterodine. The use of fesoterodine may increase the plasma concentration at a metabolism inhibition with the risk of overdose.

Halofantrine. There is an increased risk of ventricular arrhythmias, including torsade de pointes, in case of concomitant use of halofantrine with clarithromycin. If the use of this combination is obligatory, the patient should be ECG monitored.

Immunosuppressive agents. With concomitant use of immunosuppressive agents (ciclosporin, everolimus, sirolimus, tacrolimus) with clarithromycin, there is a sharp increase in their blood levels. The strict monitoring of the blood levels and monitoring of renal function should be considered. Dose adjustment may be needed.

Irinotecan. The risk of adverse effects of irinotecan increases due to increased blood levels of the active metabolite.

Lumefantrine. There is an increased risk of ventricular arrhythmias, including torsade de pointes, in concomitant use of clarithromycin and lumefantrine. The patient should be ECG monitored if the use of this combination is required.

Rivaroxaban. Increased plasma levels of rivaroxaban is associated with an increased risk of bleeding.

Tolterodine is mainly metabolized by 2D6-isoform of P450 cytochrome (CYP2D6). However, in patients without CYP2D6 the metabolism is carried out by CYP3A. In this population, the CYP3A inhibition leads to a significant increase of plasma levels of tolterodine. For these patients, the reduction of tolterodine dose may be required when used with inhibitors of CYP3A, such as clarithromycin.

Medicinal products, the concomitant use of which requires caution

Darifenacin. Concomitant use of darifenacin with clarithromycin may increase the plasma level of darifenacin that may lead to adverse reactions. Clinical observation is recommended. Dose adjustment of darifenacin may be required.

Dabigatran. There is a possibility of increasing dabigatran plasma concentrations with an increased risk of bleeding. Plasma concentration should be carefully monitored. Dose adjustment may be required.

Solifenacin. The plasma concentration of solifenacin may be increased with the risk of overdose. Plasma concentration should be carefully monitored. Dose adjustment may be required.

Tyrosine kinase inhibitors. The risk of adverse reactions of tyrosine kinase inhibitors metabolized by CYP3A are likely to be increased. The clinical observation is required while the concomitant use with clarithromycin.

Dexamethasone. There is a risk of dexamethasone plasma level increase with the risk of Cushing syndrome development.

Venlafaxine. The increase of venlafaxine plasma level is possible with the risk of overdose.

Sleeping drugs. In concomitant use with clarithromycin a slight increase of zolpidem sedation effect or a slight increase in zopiclone sedation may be observed.

Other drug interactions

Aminoglycosides. Caution is recommended in concomitant use of clarithromycin with other *ototoxic* drugs, especially with *aminoglycosides*.

Digoxin is considered to be a substrate for Pgp. Clarithromycin is known to inhibit Pgp. In concomitant use of digoxin and clarithromycin, the Pgp inhibition may lead to increased digoxin exposure. The increase of digoxin serum level in patients receiving digoxin together with clarithromycin has been reported. Some patients have shown signs of digoxin toxity including potentially fatal arrhythmias. Serum digoxin concentration should be carefully monitored in patients receiving digoxin with clarithromycin.

Zidovudine. Concomitant use of clarithromycin tablets and zidovudine in HIV-infected patients may cause decreased equilibrium concentrations of zidovudine. Clarithromycin is able to interfere with the absorption of oral zidovudine in case of concomitant use, but it substantially can be avoided by observing a 4-hour interval between each medication. The interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. Since clarithromycin when administered to adults affected zidovudine absorption after oral administration, this interaction cannot be expected when clarithromycin is administrated via intravenous infusion.

CYP3A inhibitors. There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs that are not considered to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs while administering concomitantly with clarithromycin. Increase serum levels have been reported.

Bidirectional drug interaction

Atazanavir. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) that both are CYP3A substrates and inhibitors resulted in 2-fold increase in clarithromycin exposure and 70% decrease in exposure of 14-(R)-hydroxy-clarithromycin and 28% increase in the AUC of atazanavir. Since clarithromycin has a large therapeutic range, there is no need to decrease the dose for patients with normal renal function. Clarithromycin dose should be reduced by 50% for patients with a creatinine clearance 30 to 60 ml/min and by 75% for patients with a creatinine clearance <30 ml/min. Clarithromycin doses exceeding 1000 mg per day should not be co-administrate with protease inhibitors.

Calcium channel blockers. Due of the risk of hypotension, clarithromycin simultaneously should be used with caution with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem). The interaction may increase plasma concentrations of clarithromycin and calcium channel blockers. The hypotension, bradyarrhythmias and lactic acidosis were observed in patients treated with clarithromycin and verapamil concomitantly.

Itraconazole. Both clarithromycin and itraconazole are CYP3A substrates and inhibitors. Clarithromycin may increase plasma levels of itraconazole and while itraconazole may increase plasma levels of clarithromycin. If clarithromycin is used in combination with itraconazole, the patients should be closely monitored for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir. Concomitant use of clarithromycin (500 mg twice daily) with saquinavir (soft gelatin capsules, 1200 mg three times daily), which are CYP3A substrates and inhibitors, to 12 healthy volunteers resulted in an increase in AUC of the equilibrium level at 177% and a C_{max} at 187% relative to saquinavir alone. Thus, AUC and C_{max} of clarithromycin increased approximately by 40% in comparison with the use of clarithromycin only. No dose adjustment is necessary when

both drugs are used simultaneously for a limited period of time and in the above doses/dosage forms. The results of drug interaction studies using the soft gelatin capsules may not correspond to the effects seen with saquinavir in the form of hard gelatin capsules. The results of drug interaction studies with saquinavir only may not fully reflect the effects observed in the treatment of saquinavir/ritonavir. When saquinavir is co-administered together with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

Storage and shelf life

Protected from moisture and light at a temperature not exceeding 25°C.

Keep out of the reach of children.

Shelf life is 3 years. Do not use beyond the expiration date printed on the package.

Prescription status

Prescription only medicinal product.

Packaging

500 mg in 15 ml vial for injection.

Four vials with patient information leaflet are placed in a cardboard box. Thirty-six vials with patient information leaflet are placed in a cardboard box.

Manufacturer

Manufactured by: Anfarm Hellas S.A., Greece

Carried out packaging and released quality control by: TriplePharm JLLC, 2B Minskaya St., 223141 Logoysk, Minsk region, Republic of Belarus, tel./fax: (+375) 1774 43 181,
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