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MINISTRY OF HEALTHCARE OF THE REPUBLIC OF BELARUS

Patient information leaflet
Claribaccin
Lyophilized powder
for solution for infusions 500 mg

Trade name: Claribaccin
International nonproprietary name: Clarithromycin
Pharmaceutical name: Lyophilized powder for solution for infusions 500 mg
Description: white or 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:
Pharmacodinamics
The active ingredient of Claribaccin is clarithromycin. Clarithromycin is a semisynthetic macrolide antibiotic derived by substitution of CN_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 bacteria and strains isolated from patients in the clinical practice. It shows high efficacy against many aerobic and anaerobic gram-positive and gram-negative microorganisms. The minimum inhibitory concentrations (MIC) of clarithromycin for most pathogens are generally two-fold lower than the MIC of erythromycin.
14-(R)-hydroxy metabolite of clarithromycin exhibits antimicrobial activity. For most microorganisms this metabolite is as active, or more than twice active than the starting compound, and the MICs of metabolite are twice higher the MIC of clarithromycin in relation to H. influenzae.
The data obtained *in vitro* 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* Hemofilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophila, Bordetella pertussis, Helicobacter pylori, Campylobacter jejuni; *mycoplasma*: Mycoplasma pneumoniae, Ureaplasma urealyticum; *anaerobes*: Bacteriodes fragilis (macrolide-susceptible strains), Clostridium perfringens, Peptococcus species, Peptostreptokokkus species, Propionibacterium acnes; *other microorganisms*: Chlamydia trachomatis, Mycobacterium avium, Mycobacterium leprae, Chlamydia pneumoniae.

Clarithromycin shows bactericidal properties against H.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 in the form of infusion for 30 minutes; and at doses of 500 mg, 750 mg or 1000 mg in a volume of 250 ml in the form of infusion over 60 minutes. Mean maximum concentrations (C_{max}) of clarithromycin ranged from 1.23 g/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 h·μg/ml after administration of 1000 mg. The mean value of AUC 14-(R)-hydroxy metabolite was from 2.10 h·μg/ml and 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 30 minutes and at doses of 500 mg and 750 mg in a volume of 250 ml for 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 is dependent 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 the 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. The concentration ratio in human milk to plasma concentration is 24% and 63%, respectively.

Biotransformation

Clarithromycin is converted into three metabolites: decladinosyl-clarithromycin, N-dimethyl clarithromycin and 14-(R)-hydroxy-clarithromycin. Last 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 demonstrated by the low bioavailability of the metabolite immediately after 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 lead to 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 meabolite 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% - 14-(R)-hydroxy-clarithromycin. Free clarithromycin and 14-(R)-hydroxy-clarithromycin are a large 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 starting compound. The main part of the dose of clarithromycin 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 the increase in the maximum concentration, residual concentrations, increase in the area under the curve “concentration-time” and increase in concentrations of 14-(R)-hydroxy metabolite. If the clearance was less than 30 ml/min, half-life was 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 areas under the curve “concentration-time” of clarithromycin were 2-fold higher than in the group of young people.

Therapeutic indications

- Treatment of infections caused by clarithromycin-susceptible microorganisms, if necessary, the use of parenteral therapy in adults and 12 years old children;
- Treatment of lower respiratory tract infections such as acute or chronic bronchitis, pneumonia;
- Treatment of upper respiratory tract infections, such as sinusitis or sore throat;
- Skin and soft tissue infections.

It is necessary to take into account official guidance on the proper use of antibacterial agents.

Contraindications

Hypersensitivity to macrolide antibiotics or any excipients.

The concomitant use of clarithromycin with the following medicines: astemizole, mizolastine, terfenadine, cisapride, pimozide, ivabradine, bepridil, dronedarone, sertindole (as it may lead to QT interval prolongation and the development of cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and torsade de pointes).
The concomitant use of clarithromycin with ergot alkaloids, such as ergotamine, dihydroergotamine, methylergometrin, methysergide (since it can lead to ergotoxicity).
The concomitant use of clarithromycin with midazolam for the oral administration.
The use of clarithromycin 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 interval prolongation).
The use of clarithromycin in patients with severe liver insufficiency occurring simultaneously with renal insufficiency.
The simultaneous use of clarithromycin with HMG-CoA reductase inhibitors (statins), which are largely 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 inhibitors of CYP3A4) with colchicine, ticagrelor and ranolazine.

Precautions for use

Pregnancy and lactation

Clinical safety of clarithromycin during pregnancy has not been established. Claribaccin should not be administered to pregnant women, especially in the first three months of pregnancy, except in cases where the potential benefits of its use justifies the 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 Claribaccin during lactation, the termination of breastfeeding should be considered.

Special warnings

The prolonged use of Claribaccin, 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 and *renal dysfunction*.
Clarithromycin is mainly eliminated in liver. The precautions should be observed when using the drug in patients with *impaired hepatic function*.
In the use of clarithromycin, the liver dysfunction was 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. In some cases, a liver failure was fatal, which was mainly associated with serious underlying diseases and/or concomitant medication treatment. It is necessary to stop immediately the use of clarithromycin in the event of such signs and symptoms of hepatitis as anorexia, jaundice, dark urine, itching, or abdominal pain.
When using nearly all antibacterial agents, including macrolides, there is the possibility of pseudomembranous colitis, with its severity can range from mild to life-threatening. There is also a risk of diarrhea associated with Clostridium difficile (DSKD), 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. DSKD should be assumed in all

patients with diarrhea following antibiotic use. We need a careful history selection, as the appearance of DSKD is possible more than two months after receiving antibacterial agents.
The colchicine toxicity was reported (including fatal) in the combined use of clarithromycin and colchicine, particularly in elderly patients, including patients with renal insufficiency.
The concomitant use of clarithromycin with colchicine is contraindicated.
The caution should be exercised when administering clarithromycin concomitantly with triazole benzodiazepines, 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.
Due to the risk of QT interval prolongation, clarithromycin should be used with caution in patients with coronary heart disease, severe cardiac insufficiency, hypomagnesemia, bradycardia (<50 bpm/min) or in combination with other drugs associated with QT prolongation. Claribaccin can not be used in patients with congenital or with a history of QT prolongation or with a history of ventricular arrhythmias. Co-administration of clarithromycin with other drugs that can prolong the QT interval, and with metabolized CYP3A4 isoenzym should be carried out only in exceptional cases.
It is necessary to carry out the sensitivity test when administering Claribaccin for the treatment of community-acquired pneumonia taking into account the increasing resistance of Streptococcus pneumoniae to macrolides. In the case of hospital-acquired pneumonia, clarithromycin should be used in combination with other appropriate antibiotics.
Skin and soft tissue infections of mild to moderate severity are most often caused by micro-organisms of Staphylococcus aureus and Streptococcus pyogenes. In cases where it is impossible to use the beta-lactam antibiotics, other antibiotics, such as clindamycin, may be used as drugs of first choice. Currently macrolides only play a role in the treatment of certain skin and soft tissue infections, such as infections caused by Corynebacterium minutissimum, Acne vulgaris; erysipelas; and in situations where penicillin treatment can not be used.
With the development of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS-syndrome and Henoch-Schönlein purpura, Claribaccin treatment should be discontinued immediately, and immediately begin the appropriate treatment.
Claribaccin should be used with caution in concomitant administration with inducers of cytochrome CYP3A4 enzyme.
It should be noted the possibility of cross-resistance between clarithromycin and other macrolide and 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 with concomitant use. Signs and symptoms of myopathy should be monitored. In situations where simultaneous use of clarithromycin with statins can not 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 sulfonylureas) and/or insulin can cause severe hypoglycemia. The careful monitoring of blood glucose is recommended.
In concomitant use of clarithromycin and warfarin, there is a risk of serious bleeding, a significant increase in the 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 adverse reactions of the nervous system such as seizures, dizziness, vertigo, hallucinations, confusion, disorientation, etc., which could affect the speed of psychomotor reactions.

Posology and method of administration

Claribaccin is used only intravenously. 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 then, if possible, pass to oral medicinal product.

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

Claribaccin is not 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 to 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 Claribaccin 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 lead to the formation of a precipitate. Do not use solvents containing inorganic salts or preservatives.

The resultant solution is subject to further dilution in a minimum of 250 ml of the following solvents: isotonic saline, 5% glucose solution, Ringer lactate solution.

Adverse events

When using Claribaccin, the adverse events listed below can appear (very common: ≥ 1/10; common: ≥ 1/100 - <1/10; uncommon ≥ 1/1000 - <1/100):

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

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

Immune system disorders: rare: anaphylactoid reaction, hypersensitivity; unknown: anaphylaxis, angioedema.

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

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

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, drowsiness, tremor; unknown: convulsions, ageusia, parosmiya, anosmia, paresthesia.

Cardio-vascular system disorders: common: vasodilatation; uncommon: heart failure, atrial fibrillation, prolongation of QT interval, extrasystole, palpitations; unknown: ventricular tachycardia of "pirouette" type, ventricular tachycardia, bleeding.
Respiratory system disorders: uncommon: asthma, pulmonary embolism.
Gastrointestinal disorders: common: diarrhea, vomiting, dyspepsia, nausea, abdominal pain; uncommon: oesophagitis, gastritis, stomatitis, glossitis, constipation, dry mouth, belching, flatulence; unknown: acute pancreatitis, change of tongue color, discoloration of the teeth.
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: 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: increase of 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, changes in urine color.
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, distortion of taste, abdominal pain, diarrhea, rashes, bloating, 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, analyzing their significant deviations from the standard values (i.e., a sharp increase or decrease). On the basis of this criterion, 2-3% of patients treated with clarithromycin 1000 mg daily demonstrated a significant increase in AST levels and ALT levels, as well as reducing the number of leukocytes and platelets. Several patients showed an increase in blood urea.

Overdosing

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 a patient with the history of bipolar disorder after taking 8 grams of clarithromycin.
Treatment: hemodialysis and peritoneal dialysis have no significant effect on the concentration of clarithromycin in serum, which is typical for other drugs of macrolides group. In the case of overdose, the treatment with Claribaccin must be withdrawn and the symptomatic therapy should be administered.

Drug-to-drug interactions

Drug products the concomitant use of which is contraindicated

Cisapride, pimozide, astemizole and terfenadine. Increasing of cisapride, pimozide, mizolastine, terfenadine, dronedarone, bepridil, ivabradine, sertindole levels to the serum was observed when used together with clarithromycin, which may lead to the prolongation of QT interval and occurrence of arrhythmias, including ventricular tachycardia, ventricular fibrillation and *torsades de pointes.* Similar effects were also observed in the combined use of astemizole and other macrolides.

Ergot alkaloids. Concomitant use of clarithromycin and derivatives of ergot alkaloids (ergotamine, dihydroergotamine, methylergometrin, 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 use of clarithromycin and ergot alkaloids is contraindicated.

HMG-CoA reductase inhibitors. The simultaneous use of clarithromycin with 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 is unavoidable, the therapy with lovastatin or simvastatin should be discontinued during treatment.

Clarithromycin should be administered with caution simultaneously with statins. In situations where simultaneous use of clarithromycin with statins can not be avoided, it is recommended to assign the lowest registered dose of statin. It is possible to use statin that does not depend on CYP3A metabolism (e.g. fluvastatin). Signs and symptoms of myopathy should be monitored.

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

Effect of other drugs on clarithromycin

Inducers of CYP3A. Drugs that are inducers of CYP3A (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort), can induce metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin and reduce its effectiveness. Furthermore, it may require monitoring of plasma levels of CYP3A inducer, which may be increased due to the inhibition of CYP3A by clarithromycin. The concomitant use of rifabutin and clarithromycin resulted in increased levels of rifabutin and reduction of clarithromycin levels in serum while increasing the risk of uveitis.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine. Potent inducers of cytochrome P450 enzymes such as efavirenz, nevirapine, rifampin, rifapentine and rifabutin, may accelerate the metabolism of clarithromycin, reducing its concentration in the blood plasma, but increasing the concentration of 14-(R) -hydroxy-clarithromycin - microbiologically active metabolite. Since the microbiological activity of clarithromycin and 14-(R)-hydroxy-clarithromycin varies with respect to various bacteria, the expected therapeutic effect may be lowered due to the combined 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) 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. Pharmacokinetic study has shown 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. Coadministration of ritonavir increased C_{max} of clarithromycin by 31%, C_{min} - by 182% and AUC - 77%. The complete inhibition of the formation of 14-(R)-hydroxy-clarithromycin was reported. Because of the wide range of therapeutic dose, the reduction of clarithromycin in patients with normal renal function is not required. However, the patients with renal failure require dose adjustments: the creatinine clearance of 30-60 ml/min dose of clarithromycin is necessary to reduce by 50%, with creatinine clearance <30 ml/min - 75%. Doses of clarithromycin greater than 1g/day should not be used together with ritonavir.

The same dose adjustments should be carried out in patients with impaired renal function when using ritonavir as a pharmacokinetic amplifier, along with other HIV protease inhibitors, including atazanavir and saquinavir.

Effect of clarithromycin on other medicinal products

Interactions caused by CYP3A. The combined use of clarithromycin, the known inhibitor of the CYP3A enzyme, and the drug, mainly metabolized CYP3A, may lead to increased concentrations of the latter in the plasma, which in turn may enhance or prolong its therapeutic effect and the risk of adverse reactions.

Caution should be observed when administering clarithromycin in patients receiving drug therapy - CYP3A substrates, especially if CYP3A-substrate has a narrow therapeutic range (e.g., carbamazepine) and/or substantially metabolized by this enzyme.

The change of the dose may be required and, if possible, close monitoring of serum concentrations of the drug CYP3A metabolized, in patients who used clarithromycin simultaneously.

It is known (or assumed) that the following drugs or groups of drugs are metabolized by the same CYP3A isoenzyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporin, disopyramide, alkaloids horns, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g., warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, sirolimus, terfenadine, triazolam and vinblastine, but this list is not exhausted. Such mechanism of interaction was observed with the use of phenytoin, theophylline and valproate, that are metabolized by other system isoenzyme P450of cytochrome.

Antiarrhythmics. The development of the torsade de pointes occurred during concomitant use of clarithromycin with quinidine or disopyramide. The ECG monitoring is recommended for early detection of QT interval prolongation. During therapy with clarithromycin the concentrations of these drugs should be monitored in the blood serum.

The study shows the development of hypoglycemia in concomitant use of clarithromycin and disopyramide. Therefore, close monitoring of blood glucose levels in the combined use of clarithromycin and disopyramide is required.

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. In a study of healthy patients, clarithromycin (500 mg every 8 hours) was taken with omeprazole (40 mg daily). In concomitant use of clarithromycin and omeprazole, the equilibrium plasma concentrations of omeprazole raised (C_{max}, AUC_{0-24} and $T_{1/2}$ increased by

30%, 89% and 34%, respectively). The average gastric pH value was 5.2 during the administration of omeprazole only and 5.7 during the administration of omeprazole together with clarithromycin.

Ranitidine bismuth citrate. The combined 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 clarithromycin taken together. Simultaneous treatment with clarithromycin and 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 is a slight, but statistically significant increase of theophylline or carbamazepine in the plasma concentration in concomitant use with clarithromycin. Plasma concentrations should be carefully monitored. Dose adjustment may be required.

Triazole benzodiazepines. In concomitant use of midazolam with clarithromycin tablets (500 mg twice daily) AUC of midazolam increased by 2.7 times after intravenous injection of midazolam and by 7 times after oral administration. The simultaneous use of oral midazolam and clarithromycin should be avoided. In case of intravenous use of midazolam with clarithromycin, the patient should be closely monitored for timely dose adjustment. 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), the development of clinically significant interaction with clarithromycin is unlikely.

Triazolam. The drug interactions and the development of adverse events in the central nervous system (such as drowsiness and confusion) with the combined use of clarithromycin and triazolam was reported. It is necessary to observe 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 concentrations of dopamine with the risk of overdose is possible.

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

There is an increased risk of ventricular arrhythmias in patients with congenital syndrome of QT interval 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 simultaneous use of immunosuppressive agents (cyclosporin, everolimus, sirolimus, tacrolimus) with clarithromycin, there is a sharp increase in their

concentration in the blood. The strict monitoring of the concentration in the blood, and monitoring of renal function should be carried out. Dose adjustment may be needed.
Irinotecan. The risk of adverse effects of irinotecan increases due to increased concentrations of the active metabolite in the blood.
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.
Quetiapine. The use of quetiapine and clarithromycin significantly increases the risk of quetiapine concentration and consequently the risk of overdose.
Rivaroxaban. Increased plasma concentrations 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 in plasma concentrations of tolterodine. For these patients, the reduction of tolterodine dose may be necessary when used with inhibitors of CYP3A, such as clarithromycin.
Medicinal products, the concomitant use of which requires caution
Darifenacin. In combined use of darifenacin with clarithromycin, the plasma concentration of darifenacin may be increased 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 use of clarithromycin.
Dexamethasone. Dexamethasone may increase in the plasma concentration with the risk of Cushing's syndrome development.
Venlafaxine. The increase in the concentration of venlafaxine is possible with the risk of overdose.
Sleeping drugs. In combined use with clarithromycin a slight increase of zolpidem sedation effect or a slight increase in zopiclone sedation may be observed.
Other drug interactions
Caution is advised in combined use of clarithromycin with other *ototoxic* drugs, especially with *aminoglycosides*.
Colchicine is a substrate of CYP3A isoenzyme, and protein-transporter of P-glycoprotein (Pgp). It is known that clarithromycin and other macrolides are inhibitors of CYP3A isoenzyme and Pgp. In concomitant use of clarithromycin and colchicine, the inhibition of Pgp and/or CYP3A isozyme may lead to increased exposure of colchicine. There are registered reports of colchicine toxicity when it is used concomitantly with clarithromycin, mostly in elderly patients with renal insufficiency. As reported, some cases are fatal. Concomitant use of clarithromycin and colchicine is contraindicated.
Digoxin is considered to be a substrate of P-glycoprotein (Pgp). It is known that clarithromycin is able to inhibit Pgp. In simultaneous use, the Pgp inhibition may lead to increased digoxin

exposure. It is reported the increase of digoxin concentration in blood serum of patients receiving digoxin together with clarithromycin. Some patients developed signs of digitalis intoxication, including potentially fatal arrhythmias. Digoxin concentration should be carefully monitored in the serum of patients when used with clarithromycin.

Zidovudine. Concomitant use of clarithromycin tablets and zidovudine in HIV-infected patients may cause a decrease in the equilibrium concentrations in the blood serum 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 doses of clarithromycin and zidovudine. The interaction in the administration of suspension of clarithromycin and zidovudine or dideoxyinosine in children have not been reported. Since clarithromycin when administered to adults affected zidovudine absorption after oral administration, such interaction can not be expected in case of intravenous administration of clarithromycin.

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 CYP3A (e.g. phenytoin and valproate). It is recommended to define the levels of these drugs in the blood serum while administering them with clarithromycin. The increase of their levels in the blood serum was reported.

Bidirectional interaction of drugs

Atazanavir. The use of clarithromycin (500mg twice daily) with atazanavir (400 mg once daily) that are CYP3A substrates and inhibitors, increased clarithromycin exposure in 2 times and reduced exposure of 14-(R)-hydroxy-clarithromycin by 70% and increased the AUC of atazanavir by 28%. 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 of 30-60 ml/min and by 75% for patients with a creatinine clearance <30 ml/min. Clarithromycin doses exceeding 1000 mg per day should not be used in conjunction with protease inhibitors.

Calcium channel blockers. Because 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 the plasma concentrations of clarithromycin and calcium channel blockers. The hypotension, bradyarrhythmias and lactic acidosis were observed in patients treated with clarithromycin, verapamil.

Itraconazole. Clarithromycin and itraconazole are CYP3A substrates and inhibitors, in connection with which clarithromycin may increase plasma levels of itraconazole and vice versa. If clarithromycin is used in combination with itraconazole, the patients should be closely monitored to identify the manifestations or symptoms of increased or prolonged pharmacologic effect.

Sakvinavir. The use of clarithromycin (500 mg twice daily) with saquinavir (soft gelatin capsules, 1200 mg three times a day), which are CYP3A substrates and inhibitors, in 12 healthy volunteers resulted in an increase in AUC of the equilibrium state at 177% and a C_{max} at 187% relative to saquinavir only. 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 used together with ritonavir, it is necessary to take into account the possible effects of ritonavir on clarithromycin.

Storage conditions and shelf life

Store in a dry and dark place at a temperature below 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

Medicinal product dispensable only for medical prescription.

Package

500 mg vials. 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

Manufacturer: Anarm Hellas S.A., Greece

Packer: TriplePharm JLLC, 2B Minskaya St., 223141 Logoysk, Minsk region, Republic of Belarus, Tel./fax: (+375) 1774 43 181, e-mail: triplepharm@gmail.com