

PACKAGE LEAFLET  
for medical use of a medicinal product  
**AZICIN - DARNITSA**

**Qualitative and quantitative composition:**

*active substance:* azithromycin;

1 capsule contains azithromycin dihydrate equivalent to azithromycin 250 mg;

*list of excipients:* lactose monohydrate, sodium lauryl sulfate, povidone, magnesium stearate.

**Pharmaceutical form.** Capsules.

*Basic physical and chemical properties:* hard capsules with a white cap and body. Contents of the capsule are white powder or granules.

**Pharmacotherapeutic group.** Antibacterial agents for systemic use. Macrolides, lincosamides, and streptogramins. ATC J01F A10.

**Pharmacological properties.**

*Pharmacodynamic properties.*

Azithromycin is a member of the group of macrolide antibiotics – azalides, which possess a wide spectrum of antimicrobial action. Azithromycin's mechanism of action involves inhibition of bacterial protein synthesis by binding to the 50S subunit of ribosomes and prevention of translocation of peptides in the absence of an effect on polynucleotide synthesis. Resistance to azithromycin may be primary or secondary. Complete cross resistance exists among *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis*, and *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA), to erythromycin, azithromycin, other macrolides and lincosamides.

Spectrum of antimicrobial action of azithromycin:

<b>Susceptible species</b>
<b><i>Aerobic gram-positive bacteria</i></b> <i>Staphylococcus aureus</i> (methicillin-sensitive) <i>Streptococcus pneumoniae</i> (penicillin-sensitive) <i>Streptococcus pyogenes</i> (group A)
<b><i>Aerobic gram-negative bacteria</i></b> <i>Haemophilus influenzae</i> <i>Haemophilus parainfluenzae</i> <i>Legionella pneumophila</i> <i>Moraxella catarrhalis</i> <i>Pasteurella multocida</i>
<b><i>Anaerobic bacteria</i></b> <i>Clostridium perfringens</i> <i>Fusobacterium spp.</i> (species) <i>Prevotella spp.</i> <i>Porphyromonas spp.</i>
<b><i>Other bacteria</i></b> <i>Chlamydia trachomatis</i> <i>Chlamydia pneumoniae</i> <i>Mycoplasma pneumoniae</i>
<b>Species that acquire the resistance in isolated cases</b>
<b><i>Aerobic gram-positive bacteria</i></b> <i>Streptococcus pneumoniae</i> (with intermediate sensitivity to penicillin, penicillin-resistant)

<b>Resistant species</b>
<b><i>Aerobic gram-positive bacteria</i></b> <i>Enterococcus faecalis</i> Staphylococci MRSA, MRSE* (methicillin-resistant <i>Staphylococcus aureus</i> )
<b><i>Anaerobic bacteria</i></b> Group of bacteroids <i>Bacteroides fragilis</i>

\*Methicillin-resistant *Staphylococcus aureus* has a very high prevalence of acquired macrolide resistance and is listed here due to its rare sensitivity to azithromycin.

#### *Pharmacokinetic properties.*

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma concentrations are attained in 2-3 hours after the drug administration. Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studies have shown that the concentration of azithromycin in tissues is significantly higher (50 times) than in plasma, which indicates a strong binding of the medicinal product with tissues.

Binding to serum proteins varies depending on the plasma concentration and ranges from 12% at 0.5 µg/ml to 52% at 0.05 µg/ml in serum. The apparent volume of distribution at steady state (V<sub>V<sub>ss</sub></sub>) was 31.1 L/kg.

The final plasma half-life fully reflects the tissue half-life of 2–4 days.

Approximately 12 % of the intravenous dose of azithromycin is excreted unchanged in the urine over the next three days. Particularly high concentrations of unchanged azithromycin were found in human bile. Ten metabolites have been identified in bile, which were formed by N- and O-demethylation, hydroxylation of deosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analysis showed that azithromycin metabolites are microbiologically inactive.

#### **Clinical particulars.**

##### ***Therapeutic indications.***

Infections caused by azithromycin-sensitive microorganisms:

- ENT-infections (bacterial pharyngitis/tonsillitis, sinusitis, otitis media);
- respiratory tract infections (bacterial bronchitis, community acquired pneumonia);
- skin and soft tissue infections: erythema migrans (initial stage of Lyme disease), erysipelas, impetigo, secondary pyodermatosis;
- sexually transmitted infections: uncomplicated genital infections caused by *Chlamydia trachomatis*.

##### ***Contraindications.***

- Hypersensitivity to azithromycin, any of the excipients of the drug, or any other macrolide or ketolide antibiotic.
- Severe liver and kidney disorders.
- Coadministration with ergot derivatives due to the theoretical possibility of ergotism.

##### ***Interaction with other medicinal products and other forms of interaction.***

Azithromycin should be used with caution together with other medications that may prolong the QT interval (see the section "Special warnings and precautions for use").

**Antacids.** During the study of the effects of simultaneous administration of antacids on the pharmacokinetics of azithromycin, no effect on overall bioavailability was seen, although peak plasma levels were reduced by approximately 25%. Azithromycin and antacids should not be taken simultaneously.

**Cetirizine.** In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

**Didanosine.** Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

*Digoxin.* Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin is administered concomitantly with digoxin, the possibility of elevated serum concentrations of digoxin should be considered.

*Zidovudine.* Concomitant administration of azithromycin (single doses of 1000 mg and multiple doses of 1200 mg or 600 mg) had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, the administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this phenomenon is unknown, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome metabolite complex does not occur with azithromycin.

*Ergot derivatives.* Due to theoretical possibility of ergotism, azithromycin should not be used concomitantly with ergot derivatives.

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

*Atorvastatin.* Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

*Carbamazepine.* In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

*Cimetidine.* In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

*Coumarin Type Oral Anticoagulants.* Azithromycin did not alter the anticoagulant effect of a single dose (15 mg) of warfarin in healthy volunteers. Potentiation of the anticoagulant effect has been reported after concomitant administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin type oral anticoagulants.

*Cyclosporin.* In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin  $C_{max}$  and  $AUC_{0-5}$  were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

*Efavirenz.* Concomitant administration of a single dose of azithromycin 600 mg and efavirenz 400 mg daily for 7 days did not cause any clinically significant pharmacokinetic interactions.

*Fluconazole.* Concomitant administration of a single dose of azithromycin 1200 mg did not change the pharmacokinetics of a single dose of fluconazole 800 mg. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in  $C_{max}$  (18%) of azithromycin was observed.

*Indinavir.* Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

*Methylprednisolone.* Azithromycin had no significant effect of the pharmacokinetics of methylprednisolone.

*Midazolam.* Coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

*Nelfinavir.* Administration of nelfinavir causes an increase in serum concentrations of azithromycin. Although dose adjustment of azithromycin when co-administered with nelfinavir is not recommended, careful monitoring of known side effects of azithromycin is warranted.

*Rifabutin.* Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either medicinal product. Cases of neutropenia have been reported with concomitant use of azithromycin

and rifabutin. Although neutropenia has been associated with rifabutin use, a causal relationship with azithromycin combination has not been established.

*Sildenafil.* In healthy male volunteers, there was no evidence of the effect of azithromycin (500 mg daily for 3 days) on the AUC and  $C_{\max}$  values of sildenafil or its main circulating metabolite.

*Terfenadine.* No interaction between azithromycin and terfenadine has been reported during pharmacokinetic studies. Isolated cases have been reported where the possibility of such an interaction could not be completely excluded, but there was no concrete evidence that such interaction existed.

*Theophylline.* There was no evidence of clinically significant pharmacokinetic interaction with concomitant use of azithromycin and theophylline in healthy volunteers.

*Triazolam.* Concomitant administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg of triazolam did not significantly affect the pharmacokinetic parameters of triazolam compared to triazolam and placebo.

*Trimethoprim/sulfamethoxazole.* Concomitant administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with 1200 mg of azithromycin on day 7 did not significantly affect the maximum concentrations, total exposure, or urinary excretion of trimethoprim or sulfamethoxazole. Serum azithromycin concentrations were close to those observed in other studies.

*Doxorubicin.* Clinical studies of drug interactions between azithromycin and doxorubicin have not been conducted. The clinical significance of nonclinical studies is unknown.

### ***Special warnings and precautions for use.***

*Allergic reactions.* In rare cases, azithromycin has been reported to cause serious allergic reactions, such as angioedema and anaphylaxis. Some of these reactions led to the development of recurrent symptoms and required longer follow-up and treatment.

*Impaired liver function.* Since liver is the main route of azithromycin metabolism, azithromycin should be used with extreme caution in patients with hepatic failure.

Liver function should be monitored if symptoms of liver dysfunction develop, such as asthenia, which develops rapidly and is accompanied by jaundice, dark urine, a tendency to bleed, and hepatic encephalopathy.

*Impaired renal function.* In patients with severe renal failure (glomerular filtration rate < 10 mL/min), a 33% increase in systemic exposure to azithromycin was observed.

*Cardiac arrhythmias.* Prolonged cardiac repolarization and QT interval, which increases the risk of cardiac arrhythmia and ventricular flutter-fibrillation, was observed during the treatment with other macrolide antibiotics. Similar effect of azithromycin cannot be completely excluded in patients with an increased risk of prolonged cardiac repolarisation, therefore the cautions should be exercised when prescribing treatment to patients:

- with congenital or registered prolongation of the QT interval;
- who are currently receiving treatment with other active substances known to prolong QT interval, such as class IA and III antiarrhythmic drugs, cisapride and terfenadine;
- with impaired electrolyte metabolism, particularly in cases of hypokalemia and hypomagnesemia;
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

*Myasthenia gravis.* Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

*Streptococcal infections.* Azithromycin is generally effective in the treatment of oropharyngeal inflammatory diseases caused by *Streptococcus*, but there are no data demonstrating the effectiveness of azithromycin in the prevention of acute rheumatic polyarthritis.

*Superinfections.* As with other antibacterial drugs, there is a possibility of superinfection (mycosis).

Cases of *C. difficile*-related diarrhea have been reported with almost all antibacterial agents, including azithromycin. Treatment with antibacterial agents changes the normal flora of the large intestine, which leads to excessive proliferation of *C. difficile*.

*C. difficile* produces toxins A and B, which contribute to the development of diarrhea. Hypertoxin-producing *C. difficile* strains increase the incidence rate, as these infections may be resistant to antibacterial therapy and may cause colectomy. The possibility of the development of *C. difficile*-related diarrhea should be taken into account in all patients with diarrhea that occurred after the use of

antibiotics. It is necessary to carefully analyze the medical history, as it has been reported that *C. difficile*-related diarrhea may develop 2 months after administration of antibacterial medications.

During the use of the drug, alcoholic beverages should be avoided.

AZICIN - DARNITSA contains lactose, therefore patients with rare hereditary forms of galactose intolerance, lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine.

#### *Fertility, pregnancy and lactation.*

##### Pregnancy.

There are no adequate data from use of azithromycin in pregnant women. In reproduction toxicity studies in animals the teratogenic effect of azithromycin on the fetus was not observed, but the drug was shown to pass the placenta. The safety of azithromycin administration during pregnancy has not been confirmed. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

##### Lactation.

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk. Administration of azithromycin during breast-feeding is possible only in cases where the expected benefit to the mother exceeds the potential risk to the child.

##### Fertility.

Fertility studies were conducted in rats; reduced pregnancy rates were noted following administration of azithromycin. The relevance of these data to humans is unknown.

#### *Effects on ability to drive and use machines.*

Considering the possibility of developing such adverse reactions as dizziness, drowsiness, visual disturbances, it is not recommended to use the drug when driving vehicles or using other mechanisms.

#### ***Posology and method of administration.***

AZICIN - DARNITSA should be administered in adults and children with body weight more than 45 kg. Azithromycin should be taken orally once daily at least 1 hour before or 2 hours after meals.

*For infections of the upper and lower respiratory tract, skin and soft tissues (except for chronic erythema migrans):* 500 mg (2 capsules) once a day for 3 days.

*In chronic erythema migrans:* 1 g a day (4 capsules at a time) on Day 1, from Day 2 to Day 5 – 500 mg (2 capsules) a day.

*In sexually transmitted infections:* 1 g (4 capsules) once. The course dose is 1 g.

If 1 dose of the drug is missed, it should be taken as soon as possible, and subsequent doses should be taken at 24-hour intervals.

*In case of renal impairment* with mild renal dysfunction (creatinine clearance > 40 mL/min), there is no need to change the dosage. Azithromycin should be used with caution in patients with severe renal impairment (glomerular filtration rate < 10 mL/min).

*In case of hepatic failure*, the drug should not be used in patients with severe liver diseases, since azithromycin is metabolized in the liver and excreted in the bile.

*Elderly patients* do not require dose correction.

#### *Children.*

AZICIN - DARNITSA in this dosage form should be used in children with a body weight of more than 45 kg.

Children weighing less than 45 kg should use azithromycin in a different dosage form.

#### ***Overdose.***

*Symptoms:* possible symptoms of general intoxication, hearing disorders, abdominal pain, severe nausea, vomiting, diarrhea.

*Treatment:* gastric lavage, administration of activated charcoal, symptomatic therapy aimed at maintaining the vital bodily functions. There is no specific antidote.

**Undesirable effects.**

*Eye disorders:* vision impairment.

*Ear and labyrinth disorders:* hearing impairment. Some patients taking azithromycin experienced hearing loss, deafness, and tinnitus. Most of these cases are related to experimental studies in which azithromycin was used in high doses for a long time. According to available follow-up reports, most of these disorders were reversible.

*Respiratory, thoracic and mediastinal disorders:* dyspnoea.

*Gastrointestinal disorders:* nausea, vomiting, diarrhea, abdominal discomfort (discomfort, pain, cramps), loose stools, flatulence, dyspepsia, gastritis, anorexia, constipation, discoloration of the tongue, pancreatitis.

*Hepatobiliary disorders:* hepatitis, cholestatic jaundice, including altered liver function test parameters, severe hepatitis, liver dysfunction, liver failure, fulminant hepatitis, necrotic hepatitis.

*Renal and urinary disorders:* interstitial nephritis, acute renal failure.

*Nervous system disorders:* dizziness/vertigo, hypesthesia, drowsiness, syncope, headache, seizures (also caused by other macrolide antibiotics), distortion or loss of taste and smell, ageusia, parosmia, paresthesia, asthenia, neurosis, lethargy, insomnia, sleep disorders, myasthenia gravis.

*Psychiatric disorders:* aggressiveness, psychomotor hyperactivity, anxiety, nervousness, agitation.

*Cardiac disorders:* palpitations, chest pain, paroxysmal "pirouette" type ventricular tachycardia, ventricular arrhythmia, including ventricular tachycardia (they were also found to be caused by other macrolide antibiotics); prolongation of the QT interval, ventricular flutter, hypotension.

*Blood and lymphatic system disorders:* neutropenia, leukopenia, thrombocytopenia, hemolytic anemia.

*Infections and invasions:* oral candidiasis, vaginal infections, pseudomembranous colitis.

*Skin and subcutaneous tissue disorders:* allergic reactions, including pruritus, hyperemia, rash, allergic dermatitis, conjunctivitis, angioedema, urticaria, photosensitivity; exanthema, serious skin reactions, namely: erythema polymorphic, Stevens-Johnson syndrome, toxic epidermal necrolysis.

*Musculoskeletal and connective tissue disorders:* arthralgia.

*Reproductive system and breast disorders:* impotence, vaginitis.

*Systemic disorders:* anaphylaxis, oedema, candidiasis, angioedema, anaphylactoid reactions.

*General disorders and administration site conditions:* increased fatigue, weakness, chills.

*Investigations:* lymphocytopenia, eosinophilia, decreased blood bicarbonates, increased aspartate aminotransferase, alanine aminotransferase, bilirubin, urea levels, plasma creatinine, abnormal potassium in plasma.

**Shelf life.** 3 years.

**Storage conditions.**

Keep in the original container at  $\leq 25^{\circ}\text{C}$  out of reach of children.

**Incompatibilities.**

Pharmacologically incompatible with heparin.

**Nature and contents of container.**

6 capsules in a blister; 1 blister in a carton box.

**Category of release.**

Prescription only medicine.

**Manufacturer.**

PrJSC "Pharmaceutical firm "Darnitsa".

**The manufacturer's location and address of the place of business.**

13 Boryspilska Street, Kyiv, 02093 Ukraine

**Date of last revision.**

02.10.2019



