

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

Qualitative and quantitative composition:

active substance: azithromycin;

1 tablet contains azithromycin dihydrate equivalent to azithromycin 500 mg;

List of excipients: lactose monohydrate, sodium lauryl sulfate, povidone, sodium croscarmellose, microcrystalline cellulose, magnesium stearate, talc, macrogol 4000, sepifilm 752 white.

Pharmaceutical form. Coated tablets.

Basic physical and chemical properties: oblong, white, biconvex, coated tablets.

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 inherent or acquired. 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:

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

<i>Enterococcus faecalis</i>
Staphylococci MRSA, MRSE* (methicillin-resistant Staphylococcus aureus)
Anaerobic bacteria
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 blood plasma; this indicates that the agent strongly binds to 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 (VVSS) 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 were also found 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 pyodermitosis, moderate acne vulgaris (common acne);
- 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.
- It should not be co-administered 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 and colchicine. Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates, such as digoxin or colchicine, leads to increase of serum P-glycoprotein substrate levels. Therefore, if azithromycin is administered concomitantly, the possibility of elevated serum concentrations of digoxin and colchicine 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 fact 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. Considering 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). However, postmarketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

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 no causal relationship has been established, the need for frequent monitoring of prothrombin time should be considered when prescribing azithromycin to patients receiving oral coumarin-type anticoagulants.

Cyclosporin. In a pharmacokinetic study involving healthy volunteers who took azithromycin 500 mg/day orally for 3 days, and then took a single dose of 10 mg/kg cyclosporine, a significant increase in the C_{\max} and AUC_{0-5} values of cyclosporine was found. 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 for azithromycin and doxorubicin have not been conducted. The clinical significance of these 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 (in rare cases – fatal), dermatological reactions, including acute generalized exanthematous pustulosis. 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.

If liver dysfunction is detected, azithromycin should be discontinued.

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 repolarisation and QT interval, which increases the risk of cardiac arrhythmia and ventricular flutter-fibrillation, was observed during the treatment with other macrolide antibiotics, including azithromycin. Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including *torsade de pointes*) which can lead to cardiac arrest, azithromycin should be used with caution in patients ongoing proarrhythmic conditions (especially women and elderly patients) such as 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, related with *C. difficile*. Hypertoxin-producing *C. difficile* strains increase the incidence rate, as these infections may be resistant to antibacterial therapy and may cause colectomy. Possibility of development of *C. difficile*-related diarrhea should be taken into account in all patients with diarrhea that occurs 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.

Studies of the effect on the reproductive function of animals were performed with the administration of doses corresponding to moderate toxic doses for the mother's organism. In these studies, there was no evidence of toxic effects of azithromycin on fetus. However, there are no adequate and well-controlled studies in pregnant women. Since studies of the effect on the reproductive function of animals do not always correspond to the effect in humans, azithromycin should be prescribed during pregnancy only for vital indications.

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 ENT-infections, infections of respiratory tract, skin and soft tissues (except for chronic erythema migrans): 500 mg (1 tablet) once a day for 3 days.

For acne vulgaris, the recommended total dose of azithromycin is 6 g, which should be taken according to the following scheme: 1 tablet of 500 mg once a day for 3 days with following administration of 1 tablet of 500 mg once a week for 9 weeks. The second-week dose should be taken seven days after administration of the first tablet, and the next 8 doses should be taken at 7-day intervals.

In erythema migrans: 1 g a day (2 tablets at a time) on Day 1, from Day 2 to Day 5 – 500 mg (1 tablet) a day.

In sexually transmitted infections: 1 g (2 tablets) 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 renal impairment with mild renal dysfunction (glomerular filtration rate 10-80 mL/min), the same dosage can be used as for patients with normal renal function. 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. Studies related to the treatment of such patients with azithromycin have not been conducted.

Elderly patients do not require dose correction.

Since elderly patients may be at risk for cardiac electrical conduction disorders, caution is recommended when using azithromycin due to the risk of development of cardiac arrhythmia and *torsade de pointes* arrhythmia.

Children.

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

Children and patients with body weight 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.

The following table shows undesirable effects determined using clinical studies and during post-marketing follow-up, when using all dosage forms of azithromycin in accordance with the system-organ class and frequency. Adverse reactions reported during post-marketing follow-up are shown in *italics*. Groups by frequency of manifestations were determined using the following scale: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$), very rare ($< 1/10000$); unknown (cannot be determined from available data). Within each group, according to the frequency of manifestations, adverse events are indicated in order of decreasing severity.

Adverse reactions may be or probably associated with azithromycin based on data obtained during clinical studies and post-marketing follow-up

System-organ class	Adverse reaction	Frequency
<i>Infections and invasions</i>	Candidiasis, oral candidiasis, vaginal infections, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorders, rhinitis	Uncommon
	<i>Pseudomembranous colitis</i>	Unknown
<i>Blood and lymphatic system disorders</i>	Leukopenia, neutropenia, eosinophilia	Uncommon
	<i>Thrombocytopenia, hemolytic anemia</i>	Unknown
<i>Immune system disorders</i>	Angioedema, hypersensitivity reactions	Uncommon
	<i>Anaphylactic reaction</i>	Unknown
<i>Metabolism and nutrition disorders</i>	Anorexia	Common
<i>Psychiatric disorders</i>	Nervousness, insomnia	Uncommon
	Agitation	Rare
	<i>Aggressiveness, anxiety, delirium, hallucinations</i>	Unknown
<i>Nervous system disorders</i>	Headache	Common
	Dizziness, drowsiness, dysgeusia, paresthesia	Uncommon
	<i>Syncope, convulsions, hypesthesia, increased psychomotor activity, anosmia, ageusia, parosmia, myasthenia gravis</i>	Unknown
<i>Eye disorders</i>	Vision impairment	Uncommon
<i>Ear and labyrinth disorders</i>	Hearing loss, vertigo	Uncommon
	Hearing loss, including deafness and/or tinnitus	Unknown
<i>Cardiac disorders</i>	Palpitation	Uncommon
	<i>Ventricular flutter-fibrillation (torsade de pointes), arrhythmia, including ventricular tachycardia, prolongation of the QT interval on the ECG</i>	Unknown
<i>Vascular disorders</i>	Hot flashes	Uncommon
	<i>Arterial hypotension</i>	Unknown
<i>Respiratory, thoracic and mediastinal disorders</i>	Dyspnoea, epistaxis	Uncommon
<i>Gastrointestinal disorders</i>	Diarrhea	Very common
	Vomiting, abdominal pain, nausea	Common
	Constipation, flatulence, dyspepsia, gastritis, dysphagia, dry mouth, eructation, mouth ulceration, saliva hypersecretion	Uncommon
	<i>Pancreatitis, tongue discolouration</i>	Unknown
<i>Hepatobiliary disorders</i>	Impaired liver function, cholestatic jaundice	Rare
	<i>Liver failure (rarely fatal), fulminant hepatitis, necrotic hepatitis</i>	Unknown
<i>Skin and subcutaneous tissue disorders</i>	Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis	Uncommon
	<i>Photosensitivity, acute generalized exanthematous pustulosis</i>	Rare
	<i>Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema polymorphic, drug reaction with eosinophilia and</i>	Unknown

	<i>systemic symptoms</i>	
<i>Musculoskeletal disorders</i>	Osteoarthritis, myalgia, back pain, neck pain	Uncommon
	Arthralgia	Unknown
<i>Renal and urinary disorders</i>	Dysuria, kidney pain	Uncommon
	<i>Acute renal failure, interstitial nephritis</i>	Unknown
<i>Reproductive system and breast disorders</i>	Uterine bleeding, testicular disorders	Uncommon
<i>General disorders and administration site conditions</i>	Oedema, asthenia, malaise, fatigue, face oedema, chest pain, pyrexia, pain, peripheral oedema	Uncommon
<i>Investigations</i>	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased	Common
	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubine increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium	Uncommon
<i>Lesions and poisoning</i>	Complications after the procedure	Uncommon

Information on adverse reactions that may be associated with the prevention and treatment of *Mycobacterium Avium Complex* is based on data from clinical studies and observations in the post-marketing period. These adverse reactions differ in type or frequency from those reported with the use of fast-acting dosage forms and long-acting dosage forms:

System-organ class	Adverse reaction	Frequency
<i>Metabolism and nutrition disorders</i>	Anorexia	Common
<i>Psychiatric disorders</i>	Dizziness, headache, paresthesia, dysgeusia	Common
	Hypesthesia	Uncommon
<i>Eye disorders</i>	Visual impairment	Common
<i>Ear and labyrinth disorders</i>	Deafness	Common
	Hearing loss, tinnitus	Uncommon
<i>Cardiac disorders</i>	Palpitation	Uncommon
<i>Gastrointestinal disorders</i>	Diarrhea, abdominal pain, nausea, flatulence, gastrointestinal discomfort, frequent loose stools	Very common
<i>Hepatobiliary disorders</i>	Hepatitis	Uncommon
<i>Skin and subcutaneous tissue disorders</i>	Rash, itching	Common
	Stevens-Johnson syndrome, photosensitivity	Uncommon
<i>Musculoskeletal disorders</i>	Arthralgia	Common
<i>General disorders and administration site conditions</i>	Fatigue	Common
	Asthenia, malaise	Uncommon

Shelf life.

3 years.

Storage conditions.

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

Nature and contents of container.

3 tablets in a blister; 1 blister in a carton box.

Category of release.

Prescription only medicine.

Manufacturer.

PrJSC "Pharmaceutical firm "Darnitsa".

Location of the manufacturer and address of manufacturing facilities.

13 Boryspilska Street, Kyiv, 02093 Ukraine

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