

PACKAGE LEAFLET
for medical use of a medicinal product

DOXYCYCLINE-DARNITSA

Qualitative and quantitative composition:

active substance: doxycycline;

1 capsule contains doxycycline hyclate (equivalent to doxycycline) 100 mg;

excipients: lactose monohydrate, potato starch, calcium stearate.

Pharmaceutical form. Capsules.

Basic physical and chemical properties: hard capsules with a lid and a yellow body, containing a yellow powder with a greenish tinge with white specks.

Pharmacotherapeutic group. Antibacterial agents for systemic use. Tetracycline. Doxycycline.
ATC code J01A A02.

Pharmacological properties.

Pharmacodynamics properties.

Doxycycline is a semi-synthetic antibiotic of the tetracyclines group of broad spectrum of action. It causes a bacteriostatic effect by suppressing the protein synthesis of pathogens as a result of blocking the connection of aminoacyl-transport RNA (tRNA) with the "informational RNA (mRNA) - ribosome" complex.

Doxycycline is active against Gram-positive bacteria: aerobic coccus – *Staphylococcus spp.* (including those that produce penicillinase), *Streptococcus spp.* (including *Streptococcus pneumoniae*); aerobic spore-forming bacteria – *Bacillus anthracis*; aerobic non-spore-forming bacteria – *Clostridium spp.*

Also active against Gram-negative bacteria: aerobic coccus – *Neisseria gonorrhoeae*; aerobic bacteria – *Escherichia coli*; *Shigella spp.*, *Salmonella spp.*, *Enterobacter spp.*, *Klebsiella spp.*, *Bordetella pertussis*, as well as against *Rickettsia spp.*, *Treponema spp.*, *Mycoplasma spp.*, *Chlamydia spp.*

Resistant to doxycycline: *Pseudomonas aeruginosa*, *Proteus spp.*, *Serratia spp.*, most strains of *Bacteroides fragilis*.

Pharmacokinetics properties.

The medicinal product is readily absorbed from the digestive tract, almost regardless of the presence of food. The plasma protein binding is 80–90 %. The maximum concentration in blood plasma is achieved 2 hours after medicinal product administration. Depending on the dose, the therapeutic concentration of doxycycline in the blood is maintained for 18–24 hours. It is rapidly distributed in most body fluids, including bile, paranasal sinuses, pleural, synovial, and ascitic fluids. The concentration in the cerebrospinal fluid varies and after parenteral administration can be 10–25 % of the concentration in the blood serum. Eliminated slowly. Elimination half-life of the medicinal product is 12–22 hours. A significant part of doxycycline is excreted unchanged in the faeces and about 40 % in the urine.

Clinical particulars.

Therapeutic indications.

Doxycycline has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms:

- *respiratory tract infections*: pneumonia and other diseases of the lower respiratory tract caused by susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenza*, *Klebsiella pneumoniae*; pneumonia caused by *Mycoplasma pneumoniae*; chronic bronchitis, sinusitis;
- *urinary tract infections*: infections caused by susceptible strains of *Klebsiella*, *Enterobacter*, as well as bacteria *Escherichia coli*, *Streptococcus faecalis*;
- *sexually transmitted infections*: infections caused by *Chlamydia trachomatis*, including uncomplicated urethral, endocervical infections and rectal infections; non-gonococcal urethritis caused by *Ureaplasma urealyticum* (*T-mycoplasma*); chancroid, granuloma inguinale, venereal granuloma; the medicinal product is an alternative in the treatment of gonorrhea and syphilis;
- *skin infections*: acne, when antibiotic therapy is considered necessary.

The treatment of infections caused by microorganisms which respond to other tetracyclines, such as:

- *ophthalmic infections*: infections caused by susceptible bacteria *gonococci*, *staphylococci* and *Haemophilus influenza*. Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. The paratrachoma, may be treated with doxycycline alone or in combination with other medicinal products;
- *rickettsial infections*: typhus group, Rocky Mountain spotted fever, coxiellosis, tick-bite fever, *Coxiella* endocarditis;
- *other infections*: ornithosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse-borne relapsing fever, tick-borne relapsing fever, tularemia glanders, chloroquine-resistant falciparum malaria and acute intestinal amebiasis (in combination with an amebicide).

Prophylaxis in the following conditions: Scrub typhus, travelers' diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis and malaria. Prevention of malaria should be used in accordance to current guidelines, as resistance is an ever changing problem.

An alternative treatment: leptospirosis, gas gangrene, tetanus.

Contraindications.

Hypersensitivity to tetracyclines or to other components of the medicinal product; porphyria; severe liver failure; leukopenia.

Interaction with other medicinal products and other forms of interaction.

In case of concomitant use of medicinal product with other medicinal products, it is possible:

with *antacids* (aluminum, calcium, magnesium), kaolin, magnesium-containing laxatives, sodium bicarbonate, medicinal products of iron and zinc, sucralfate, cholestyramine, cholestipol – the absorption of doxycycline may be impaired;

with *barbiturates*, carbamazepine, primidone, rifampicin, phenytoin – a decrease in plasma concentrations and a reduction in the half-life ($T_{1/2}$) of doxycycline (induction of monooxygenases and acceleration of biotransformation), which can lead to a decrease in the antibacterial effect;

with *anticoagulants*, *indirect anticoagulants* – potentiation of the effect of the latter; it may be necessary to reduce the dose of anticoagulants;

with *cyclosporine* – may increase the plasma concentration of cyclosporine in blood plasma; co-administration should only be undertaken with appropriate monitoring;

with *methoxyflurane* – fatal renal toxicity;

with *retinoids* – increased risk of intracranial hypertension; this combination should not be used;

with *methotrexate* – increasing the toxicity of the latter; this combination should be used with caution;

with *hormonal contraceptives* – reducing their effectiveness and increasing the frequency of breakthrough bleeding when taking estrogen-containing oral contraceptives;

with *penicillins* – reducing the effectiveness of the latter;

with *oral vaccines against typhoid fever* – reducing the effectiveness of the latter; this combination should not be used.

Concomitant use of isotretinoin or other systemic retinoids and doxycycline should be avoided. Each of

these agents used alone has been associated with benign intracranial hypertension (pseudotumour cerebri).

Special warnings and precautions for use.

To reduce stomach irritation, the medicinal product should be taken with food, drinking plenty of water. With long-term use of the medicinal product, the composition of peripheral blood should be regularly monitored, functional liver tests should be performed, and the content of urea in the blood serum should be determined.

In the treatment of infections caused by β -hemolytic group A *streptococci*, the duration of treatment should be at least 10 days.

When treating sexually transmitted diseases with suspected concomitant syphilis, appropriate diagnostic procedures, including dark field microscopy and other tests, should be employed. In such cases, monthly serological tests should be performed for at least 4 months.

Use the medicinal product with caution in patients with impaired liver function or people who are receiving potentially hepatotoxic drugs. Hepatic impairment associated with oral or parenteral of tetracyclines, including doxycycline, has been reported extremely rarely.

Use the medicinal product with caution in patients with myasthenia gravis because drugs of the tetracyclines group, including doxycycline, can cause mild neuromuscular blockade.

Renal excretion of doxycycline in patients with normal renal function is approximately 40 % in 72 hours. This range can be reduced to 1–5 % within 72 hours in people with severe renal insufficiency (creatinine clearance below 10 ml/min). Studies have not shown a significant difference in the half-life of doxycycline from serum in patients with normal and impaired renal function. Hemodialysis does not affect the serum half-life of the.

The antianabolic action of tetracyclines can lead to an increase in blood urea levels. The antianabolic effect was not observed with the use of doxycycline in patients with impaired renal function.

Photosensitivity reactions have been observed in some patients taking tetracycline, including doxycycline. During doxycycline treatment and for 4–5 days after its completion, it is recommended to protect exposed areas of the body from direct sunlight and artificial UV-radiation. Treatment with tetracyclines, including doxycycline, should be discontinued immediately at the first signs of erythema on the skin.

Treatment with antibacterial medicinal products can lead to overgrowth of insensitive microorganisms, including microorganisms of the genus *Candida*. To prevent the development of candidiasis, it is recommended to use antifungal drugs simultaneously with doxycycline.

Treatment with antibacterial medicinal products alters the normal flora of the large intestine, resulting in an overgrowth of insensitive microorganisms, including *Clostridium difficile*. Cases of *Clostridium difficile*-induced diarrhea have been reported with almost all antibacterial drugs. Diarrhea can range from mild to life-threatening. Patients taking antibacterial medicinal products should be closely monitored because *Clostridium difficile*-associated diarrhea may occur within two months of administration antibacterial medicinal products.

Pseudomembranous colitis has been reported in some patients taking antibacterial medicinal products, including doxycycline. The severity of this complication ranged from mild to life-threatening. It is necessary to consider this diagnosis in patients presenting with diarrhea as a result of the use of antibacterial drugs.

Esophagitis and esophageal ulcers have been reported in some patients taking encapsulated or tablet forms tetracycline class, including doxycycline. Most of these patients administered the medicinal product just before bedtime or with insufficient fluid.

Mild intracranial hypertension and protrusion of the umbilicus have been reported in neonates who received the medicinal product at the maximum therapeutic dose. These complications quickly disappeared after discontinuation of the medicinal product.

When examining a biopsy of the thyroid gland in patients who have been taking doxycycline for a long time, it is possible to stain the tissue in the micropreparations in a dark brown color.

The use of tetracyclines can lead to an exacerbation of the course of systemic lupus erythematosus.

Serious skin reactions such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic manifestations (DRESS) have been reported in patients receiving doxycycline. If serious skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be prescribed.

The occurrence of photoonycholysis has been reported in patients taking doxycycline.

Benign intracranial hypertension (pseudotumour cerebri) has been associated with the use of tetracyclines (including doxycycline). Benign intracranial hypertension (pseudotumour cerebri) is usually transient, but irreversible vision loss due to benign intracranial hypertension (pseudotumour cerebri) has been reported with tetracyclines (including doxycycline). In case of visual impairment during treatment, an immediate ophthalmological examination is required. Because intracranial pressure may remain elevated for several weeks after discontinuation of the medicinal product, patients should be monitored until their condition stabilizes. Concomitant use of isotretinoin, as with other systemic retinoids, with doxycycline should be avoided, as it is known that isotretinoin can also cause benign intracranial hypertension (pseudotumour cerebri).

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Do not drink alcohol during treatment.

The medicinal product contains lactose, therefore patients with rare hereditary forms of galactose intolerance, lactase deficiency or glucose-galactose malabsorption syndrome cannot use medicinal product.

Fertility, pregnancy and lactation.

The medicinal product is contraindicated during pregnancy because the use of tetracyclines during dental development (during pregnancy) can cause a permanent discoloration of the teeth (yellow-brown-gray). This adverse reaction is more common with long-term use, but can also occur during repeated short courses of treatment. Enamel hypoplasia has also been reported.

The medicinal product is contraindicated during breastfeeding because tetracyclines pass into breast milk.

Effects on ability to drive and use machines.

Until the individual patient's response to the drug has been clarified, one should refrain from driving vehicles or working with mechanisms, since during treatment with doxycycline, visual impairment, dizziness, arterial hypertension, ringing in the ears, blurred vision, scotoma, diplopia, long-term vision loss may occur.

Posology and method of administration.

The medicinal product is administered orally during or after a meal (can be washed down with milk or kefir).

Adults and children over 12 years old weighing more than 45 kg.

On the first day of treatment of acute infections, the daily dose is 200 mg once or 100 mg with an interval of 12 hours, in the following days – 100 mg. In the treatment of severe infections, the medicinal product should be used at a dose of 200 mg per day during the entire period of treatment.

The duration of the course of treatment is determined by the doctor individually, continuing treatment for at least 24–48 hours after the disappearance of symptoms and normalization of body temperature.

Children over 12 years old weighing more than 45 kg.

On the first day of treatment, the daily dose of the medicinal product is 4.4 mg/kg body weight (for 1 or 2 doses), on the following days – 2.2 mg/kg body weight (for 1 or 2 doses). In the treatment of severe infections, a dose of 4.4 mg/kg body weight may be prescribed for the entire period of treatment.

Special cases of administration.

Acne: the medicinal product should be used in a dose of 50 mg per day for 6–12 weeks.

Sexually transmitted infections:

- uncomplicated cervical infections, urethral, rectal infections caused by *Chlamydia trachomatis*; uncomplicated genital infections caused by *Neisseria gonorrhoeae* (exception – anorectal infections in men); urethritis caused by *Ureaplasma urealyticum*: the medicinal product should be used in a dose of 100 mg twice a day for 7 days;
- orchepididymitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*: the medicinal product should be used in a dose of 100 mg twice a day for 10 days;
- primary and secondary syphilis in patients without confirmed pregnancy and with penicillin allergy (as an alternative treatment): the medicinal product should be used in a dose of 200 mg twice a day for 14 days.

Louse-borne relapsing fever, tick-borne relapsing fever: the medicinal product should be used in a dose of 100–200 mg once depending on the severity of the disease.

Chloroquine-resistant falciparum malaria: the medicinal product should be used in a dose of 200 mg per day for at least 7 days.

Prophylaxis of malaria: the medicinal product is prescribed in a dose of: adults – 100 mg per day, children over 12 years – from 2.2 mg/kg body weight per day to a total dose of 100 mg per day. Prophylaxis can begin 1–2 days before traveling to a region with malaria. Prophylactic use of the medicinal product should be continued daily during travel in the malarial areas and for 4 weeks after the traveler leaves the malarial area. Current malaria treatment standards should also be considered.

The prevention of scrub typhus: The medicinal product should be used in a dose of 200 mg once.

The prevention of travelers' diarrhoea in adult: the medicinal product should be used: on the first day of the trip – at a dose of 200 mg once or 100 mg with an interval of 12 hours; during the next days of travel – in a dose of 100 mg. Data on the use of the medicinal product prophylactically are not available beyond 21 days.

The prevention of leptospirosis: the medicinal product should be used in a dose of 200 mg once a week during the entire stay in the region with leptospirosis and 200 mg of the medicinal product at the end of the trip. Data on the use of the medicinal product prophylactically are not available beyond 21 days.

Special groups of patients:

- elderly patients: the medicinal product can be used in the usual dosages with no special precautions. Doxycycline-Darnitsa may be the medicinal product of choice for elderly patients, as its use is less associated with the development of irritation and esophageal ulcers;
- patients with renal failure: the use of the medicinal product in the recommended doses does not lead to the cumulation of antibiotics (see section "Special warnings and precautions for use");
- patients with hepatic impairment: see section "Special warnings and precautions for use".

Children.

The medicinal product is contraindicated for use in children under the age of 12 years.

Like other tetracyclines, doxycycline forms stable calcium complexes in any bone-forming tissue. A decrease in the level of growth of the fibula was observed in premature infants who received oral tetracycline at a dose of 25 mg/kg of body weight every 6 hours. This adverse reaction is reversible when the medicinal product is discontinued.

The use of tetracyclines during the development of teeth (children under 12 years) can cause a permanent discoloration of the teeth (yellow-brown-gray). This adverse reaction is more common with long-term use, but can also occur during repeated short courses of treatment. Enamel hypoplasia has also been reported.

Overdose.

Symptoms: intensification of adverse reactions.

Treatment: medicinal product withdrawal, gastric lavage, supportive and symptomatic therapy.

Hemodialysis is ineffective.

Undesirable effects.

Ear and labyrinth disorders: tinnitus.

Gastrointestinal disorders: dyspepsia, abdominal pain, dysphagia, nausea, vomiting, diarrhea. Esophagitis and ulceration have been reported in patients taking doxycycline capsules and tablets. Colitis caused by the microorganism *Clostridium difficile*, enterocolitis, inflammatory lesions (with monilial growth) in the anogenital area.

Hepatobiliary disorders: there have been reports of isolated cases of hepatotoxicity with a temporary increase in liver function, liver dysfunction, jaundice, hepatitis, liver failure, pancreatitis.

Renal and urinary disorders: an increase in the level of urea in the blood, an increase in the level of residual urea nitrogen.

Endocrine disorders: with long-term use of tetracyclines, a brown-black color of the micropreparation of the thyroid tissue was observed. No thyroid dysfunction was detected.

Metabolism and nutrition disorders: anorexia.

Nervous system disorders: headache, dizziness, protrusion of the umbilicus in newborns, benign intracranial hypertension (pseudotumour cerebri), symptoms of which included blurred vision, scotoma, and diplopia, have been reported to cause irreversible vision loss.

Cardiac disorders: arterial hypotension, tachycardia, pericarditis, hot flashes, Schonlein-Henoch disease, dyspnea.

Blood and lymphatic system disorders: eosinophilia, hemolytic anemia, thrombocytopenia, neutropenia, porphyria.

Immune system disorders: hypersensitivity reactions, including anaphylaxis, anaphylactoid reactions, anaphylactic shock, anaphylactoid purpura, urticaria, angioneurotic edema, exacerbation of systemic lupus erythematosus, serum sickness, dyspnea, peripheral edema.

Skin and subcutaneous tissue disorders: skin rashes, including maculopapular and erythematous rashes; erythema multiforme, skin photosensitivity reactions, photoonycholysis, exfoliative dermatitis, Stevens-Johnson syndrome (malignant exudative erythema), Lyell's syndrome (toxic epidermal necrolysis), drug rash with eosinophilia and systemic manifestations (DRESS).

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

Infections and invasion: doxycycline treatment can lead to the development of superinfections, such as staphylococcal enterocolitis, pseudomembranous colitis, candidiasis of the skin and mucous membranes with the following manifestations: inflammation of the mucous membrane of the mouth and throat (glossitis, stomatitis), acute inflammation of the external genitalia and vagina in women (vulvovaginitis), inflammation of the anogenital area.

Other: staining and hypoplasia of tooth enamel with prolonged use of the medicinal product.

Shelf life. 2 years.

Special precautions for storage.

Store in the original packaging at temperature not above 25 °C.

Keep out of reach of children.

Nature and contents of container.

10 capsules in a blister; 1 or 2 blisters in a pack; 1 000 capsules in plastic containers.

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.

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