

**APPROVED**  
**by the Order of the Ministry of**  
**Health of Ukraine**  
**28.04.2017 No. 478**  
**Marketing Authorization**  
**No. UA/6338/01/01**  
**UA/6338/01/02**

**VARIATIONS APPLIED**  
**By the Order of the Ministry of**  
**Health of Ukraine**  
**31.10.2019 No. 2205**

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

**CEFOTAXIM-Darnitsa**

***Qualitative and quantitative composition:***

*active substance:* cefotaxime;

1 vial contains cefotaxime sodium equivalent to cefotaxime 1 g.

**Pharmaceutical form.** Powder for solution for injection.

*Main physical and chemical properties:* white or slightly yellowish crystalline powder, hygroscopic.

**Pharmacotherapeutic group.** Antibacterials for systemic use. Other beta-lactam antibacterials. Third-generation cephalosporins. Cefotaxime.  
ATC code J01D D01.

***Pharmacological properties.***

*Pharmacodynamic properties.*

Cefodax-Darnitsa is a III generation semi-synthetic cephalosporin antibiotic for parenteral use. It has a bactericidal effect. Cefotaxime has a wide range of action.

Sensitive to the medicinal product: *Streptococci* (except group D), including *Streptococcus pneumoniae*; *Staphylococcus aureus*, incl. penicillinase-forming and non-penicillinase-forming strains; *Bacillus subtilis* and *mycoides*; *Neisseria gonorrhoeae* (penicillinase-forming and non-penicillinase-forming strains), *Neisseria meningitidis*, other *Neisseria species*; *Escherichia coli*; *Klebsiella spp.*, including *Klebsiella pneumoniae*; *Enterobacter spp.* (some strains are resistant); *Serratia spp.*; *Proteus* (indole-positive and indole-negative species); *Salmonella*; *Citrobacter spp.*; *Providencia*; *Shigella*; *Yersinia*; *Haemophilus influenzae* and *parainfluenzae* (penicillinase-forming and non-penicillinase-forming strains, including resistant to ampicillin); *Bordetella pertussis*; *Moraxella*; *Aeromonas hydrophilia*; *Veillonella*; *Clostridium perfringens*; *Eubacterium*; *Propionibacterium*; *Fusobacterium*; *Bacteroides spp.* and *Morganella*.

The following are inconstantly sensitive to the action of the medicinal product: *Pseudomonas aeruginosa*; *Acinetobacter*; *Helicobacter pylori*; *Bacteroides fragilis* i *Clostridium difficile*.

Resistant to the medicinal product: *Streptococcus* group D, *Listeria* and methicillin-resistant staphylococci.

*Pharmacokinetic properties.*

*Absorption.* Five minutes after a single intravenous injection of 1 g of cefotaxime, its serum

concentration is 100 µg/ml. After intramuscular administration of cefotaxime in the same dose, the maximum concentration in the blood is reached after 0.5 hours and is 24 µg/ml. The bactericidal concentration in the blood persists for 12 hours.

**Distribution.** Plasma protein binding is on average 25-40 %. Cefotaxime penetrates well into tissues and body fluids. It is determined in effective concentrations in pleural, peritoneal, synovial fluids. Penetrates the blood-brain barrier. Biotransformed with the formation of the active metabolite.

**Excretion.** Approximately 60-70 % of the administered dose of the medicinal product is excreted in the urine unchanged, and the rest is excreted in the form of metabolites. Partially excreted in the bile. The half-life of the medicinal product is 1 hour for intravenous administration and 1-1.5 hours for intramuscular administration. In renal failure and in elderly patients, the half-life of the medicinal product increases by about 2 times. In newborns, the half-life of the medicinal product is from 0.75 to 1.5 hours, and in premature infants - from 1.4 to 6.4 hours.

### **Clinical particulars.**

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

Infections caused by drug-sensitive microorganisms:

- infections of ENT organs (sore throat, otitis);
- respiratory tract infections (bronchitis, pneumonia, pleurisy, abscesses);
- urogenital infections;
- septicemia, bacteremia;
- intra-abdominal infections (including peritonitis);
- skin and soft tissue infections;
- bone and joint infections;
- meningitis (with the exception of listeria) and other infections of the central nervous system.

Prevention of infections after surgical operations on the digestive tract, urological and obstetric-gynecological operations.

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

Hypersensitivity to cephalosporin antibiotics and to other beta-lactam antibiotics, hypersensitivity to lidocaine (intramuscular injection); bleeding, history of enterocolitis (especially nonspecific ulcerative colitis).

AV-blockade without an established pacemaker, severe heart failure.

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

Concomitant use with *nephrotoxic medicinal products* (aminoglycosides) and potent *diuretics* (ethacrynic acid, furosemide), *colistin*, *polymyxin*, the risk of developing renal failure increases.

During treatment with cefotaxime, the effectiveness of *oral contraceptives* may decrease, so during this period it is necessary to use additional contraception. Cefotaxime should not be used in conjunction with bacteriostatic antibiotics (e.g. *tetracyclines*, *erythromycin* and *chloramphenicol*) as an antagonistic effect is possible.

In combination therapy, cefotaxime solutions should not be mixed with aminoglycoside solutions - they must be administered separately.

Concomitant use of *nifedipine* increases the bioavailability of cefotaxime by 70 %.

*Probenecid* blocks the tubular secretion of cefotaxime and prolongs its half-life.

Cefotaxime should not be used with *lidocaine*:

- with intravenous administration;
- children under 30 months;
- patients with a history of hypersensitivity to lidocaine;
- patients with heart block.

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

Prescribe with caution in case of impaired renal or liver function, with a history of hypersensitivity to penicillins. In case of impaired renal function, the dose of the medicinal product should be reduced taking into account the severity of renal failure and the sensitivity of the pathogen. With long-term use of the medicinal product, kidney function should be monitored, and dysbiosis should be prevented. It is advisable to regularly monitor the cellular composition of peripheral blood, liver function. When using the medicinal product, it is possible to develop a false-positive Coombs test.

*Anaphylactic reactions.* The use of cephalosporins requires clarification of the allergic history (allergic diathesis, hypersensitivity reactions to beta-lactam antibiotics). If the patient develops a hypersensitivity reaction, treatment should be discontinued. The use of cefotaxime is strictly contraindicated in patients with a history of an immediate hypersensitivity reaction to cephalosporins. In case of any doubt, the presence of a doctor at the first administration of the medicinal product is mandatory due to the possible development of an anaphylactic reaction. Known cross-allergy between cephalosporins and penicillins, which occurs in 5-10% of cases. In patients with a history of penicillin allergy, the medicinal product should be used with extreme caution.

*Pseudomembranous colitis.* In the first weeks of treatment, pseudomembranous colitis may occur, manifested by severe prolonged diarrhea. The diagnosis is confirmed by colonoscopy and/or histological examination. These complications are regarded as very serious: the medicinal product should be discontinued immediately and adequate therapy should be prescribed, including oral vancomycin or metronidazole. The combination of the use of cefotaxime with nephrotoxic medicinal products requires monitoring of renal function, the use of more than 10 days - monitoring of blood composition. Elderly and debilitated patients should be prescribed vitamin K (prevention of hypocoagulation).

As with other broad-spectrum antibiotics, long-term use can lead to an increased growth of insensitive microorganisms, which requires discontinuation of treatment. If superinfection occurs during treatment, antimicrobial therapy should be used. False-positive results can be obtained when urine glucose is measured by the recovery method. An enzyme test should be used to prevent this.

During treatment, alcohol should not be consumed, since effects similar to the action of disulfiram are possible (flushing of the face, cramps in the abdomen and stomach area, nausea, vomiting, headache, lowering blood pressure, tachycardia, difficulty breathing).

1 g of powder for solution for injection contains 2.2 mmol (50.5 mg) sodium. The amount of sodium at the maximum daily dose exceeds 8.7 mmol (200 mg). This should be taken into account in patients on a sodium diet.

#### *Fertility, pregnancy and lactation*

The use of the medicinal product during pregnancy is contraindicated.

Breast-feeding should be discontinued during treatment with the medicinal product.

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

Due to the possibility of adverse reactions from the nervous system, you should avoid driving or working with other mechanisms during the treatment period.

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

The medicinal product is used for intravenous jet injection and drip and intramuscular administration. For intravenous jet injection, 1 g of powder is dissolved in 8 ml of sterile water for injections. Inject slowly during 3-5 minutes.

For intravenous infusion, dissolve 1 g of powder in 50 ml of 0.9% sodium chloride solution or 5% glucose solution. The duration of the infusion is 50-60 minutes.

For intramuscular administration, 1 g of powder is dissolved in 4 ml of sterile water for injection or 1% lidocaine solution and administered deep into the gluteal muscle.

The duration of the course of treatment is determined by the doctor individually.

For adults and children weighing 50 kg or more, appoint Cefodar-Darnitsa at a dose of 1 g every 12

hours. In severe cases, prescribe the medicinal product in a dose of 1 g 3-4 times a day. The maximum daily dose is 12 g.

For uncomplicated infections, as well as for urinary tract infections, administer intramuscularly or intravenously at a dose of 1 g every 12 hours;

for uncomplicated acute gonorrhea, administer 1 g intramuscularly 1 time per day or intravenously;

for infections of moderate severity, prescribe the medicinal product in a dose of 1-2 g every 12 hours;

for severe infections (meningitis), administer 2 g of the medicinal product intravenously every 6-8 hours.

For children weighing up to 50 kg, the medicinal product should be prescribed at a dose of 50-100 mg/kg per day, divided into 3-4 intramuscular or intravenous injections. In severe infections (including meningitis), the daily dose should be increased to 100-200 mg/kg body weight and administered 4-6 times intravenously or intramuscularly.

For premature infants and children up to the 1st week of life, the daily dose of the medicinal product is 50 mg/kg of body weight, divided into two equal doses, administered intravenously.

For children 1-4 weeks of life, the daily dose of the medicinal product is 50-100 mg/kg body weight, divided into three dose levels, administered intravenously.

When preventing the development of infections before surgery with the introduction of anesthesia, 1 g of Cefodar-Darnitsa should be administered once. If necessary, repeat the dose in 6-12 hours.

In case of impaired renal function, the dose of the medicinal product should be reduced. With a creatinine clearance of 10 ml/min or less, the daily dose of the medicinal product should be halved.

#### *Children.*

Do not prescribe the medicinal product intramuscular to children under 2.5 years of age.

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

*Symptoms:* fever, leukopenia, thrombocytopenia, acute hemolytic anemia, skin, gastrointestinal and liver reactions, shortness of breath, renal failure, stomatitis, anorexia, temporary hearing loss, loss of spatial orientation in space, encephalopathy (especially in renal failure) are possible. In rare cases, convulsions are observed, as well as increased side effects.

*Treatment.* There is no specific antidote. Serum cefotaxime levels can be reduced by hemodialysis or peritoneal dialysis. If necessary, carry out symptomatic therapy.

If anaphylactic shock occurs, appropriate measures should be taken immediately. At the first signs of hypersensitivity reactions (skin rash, urticaria, headache, nausea, loss of consciousness), cefotaxime should be discontinued. In case of a severe hypersensitivity reaction or anaphylactic reaction, appropriate therapy should be initiated (administration of epinephrine and/or glucocorticoids). In other clinical conditions, additional measures may be required, for example, artificial respiration, the use of histamine receptor antagonists. In case of vascular insufficiency, resuscitation measures should be taken.

#### ***Undesirable effects.***

*Gastrointestinal disorders:* nausea, vomiting, diarrhea, flatulence, abdominal pain, dysbiosis, rarely - stomatitis, glossitis, pseudomembranous colitis.

*Hepatobiliary disorders:* hepatitis, acute hepatic failure, liver dysfunction, jaundice, cholestasis.

*Nervous system disorders:* headache, dizziness, convulsions, reversible encephalopathy, fatigue, weakness.

*Blood and lymphatic system disorders:* granulocytopenia, neutropenia, transient leukopenia, thrombocytopenia, agranulocytosis, anisocytosis, eosinophilia, hypoprothrombinemia, hemolytic anemia, hypocoagulation.

*Immune system disorders:* hypersensitivity reactions, including hyperemia, rash, skin itching, urticaria, bronchospasm, exudative erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), fever, anaphylactic reactions, angioedema, rare – anaphylactic shock.

*General disorders and administration site conditions:* pain and infiltrate at the site of intramuscular injection, pain along the vein, tissue inflammation, phlebitis.

*Biochemical parameters:* an increase in the level of hepatic transaminases, lactate dehydrogenase, alkaline phosphatase and bilirubin, the concentration of urea nitrogen and creatinine, a positive Coombs reaction.

*Effects due to biological action:* development of superinfection is possible (including candidosis, vaginitis).

*Other:* bleeding and hemorrhage, autoimmune hemolytic anemia, interstitial nephritis, arrhythmias (with rapid jet injection).

When treating infections caused by the spirochete, complications such as Herxheimer's reaction can occur. This can lead to fever, chills, headaches and joint pain.

#### Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after registration of the medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective medicinal product. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

#### ***Shelf life***

3 years.

#### **Special precautions for storage**

Store in the original package at temperature not above 25 °C. Keep out of the reach of children.

#### ***Incompatibilities.***

Solution of the medicinal product is incompatible with aminoglycoside solutions in a same syringe or dropper. For dilution, use the solutions listed in the section "Posology and method of administration".

#### **Nature and contents of container.**

1 g of powder in vial; 1, 5, 40 vials in a package.

1 vial of 1 g of powder and 1 ampoule of solvent (Water for injection-Darnitsa in an ampoule of 10 ml) in a package.

**Category of release.** Prescription only.

**Manufacturer** PrJSC “Pharmaceutical Firm “Darnitsa”

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

13, Boryspilska Street, Kyiv, 02093, Ukraine.

#### **Date of the last revision.**

31.10.2019