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VARIATIONS APPLIED
By the Order of the Ministry of
Health of Ukraine
15.07.2020 No. 1609

PACKAGE LEAFLET
for medical use of a medicinal product

CEFUROXIM-DARNITSA

Qualitative and quantitative composition:

active substance: cefuroxime;

1 vial contains cefuroxime sodium salt equivalent to cefuroxime 0.75 g or 1.5 g.

Pharmaceutical form. Powder for solution for injection.

Main physical and chemical properties: white or almost white powder with a yellowish or creamy tinge, slightly hygroscopic.

Pharmacotherapeutic group. Antibacterials for systemic use. Other β -lactam antibacterials. Second-generation cephalosporins. Cefuroxime.
ATC code J01D C02.

Pharmacological properties.

Pharmacodynamic properties.

Second-generation cephalosporin antibiotic for parenteral use. Acts bactericidal, disrupts the synthesis of the cell wall of microorganisms. Has a wide range of action. Resistant to most β -lactamases, therefore, respectively, shows activity against many ampicillin- or amoxicillin-resistant strains.

Highly active against:

- gram-negative aerobes (*Escherichia coli*, *Klebsiella spp.*, *Proteus mirabilis*, *Proteus rettgeri*, *Providencia spp.*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae* (including ampicillin-resistant strains), *Moraxella (Branhamella) catarrhalis*, *Neisseria gonorrhoeae* (including strains that produce penicillinase), *Neisseria meningitidis*, *Salmonella spp.*;
- gram-positive aerobes (*Staphylococcus aureus*, *Staphylococcus epidermidis* (including penicillinase-producing strains but excluding methicillin-resistant strains)), *Streptococcus pyogenes* (as well as other β -hemolytic streptococci), *Streptococcus pneumoniae*, group B *Streptococcus (Streptococcus agalactiae)*, *Streptococcus mitis (viridans variety)*, *Bordetella pertussis*);
- anaerobes;
- gram-positive and gram-negative cocci (including *Peptococcus* and *Peptostreptococcus species*);
- gram-positive bacteria (including most *Clostridium spp.*) and gram-negative bacteria (including *Bacteroides spp.* and *Fusobacterium spp.*), *Propionibacterium spp.*;
- other microorganisms: *Borrelia burgdorferi*.

Microorganisms insensitive to cefuroxime: *Clostridium difficile*, *Pseudomonas spp.*, *Campylobacter spp.*, *Acinetobacter calcoaceticus*, *Listeria monocytogenes*, methicillin-resistant strains of *Staphylococcus aureus*, methicillin-resistant strains of *Staphylococcus epidermidis*, *Legionella spp.*

Some strains of microorganisms non-susceptible to cefuroxime: *Enterococcus* (*Streptococcus*) *faecalis*, *Morganella morganii*, *Proteus vulgaris*, *Enterobacter spp.*, *Citrobacter spp.*, *Serratia spp.*, *Bacteroides fragilis*.

Pharmacokinetic properties.

Following intramuscular administration of 0.75 g, the maximum serum concentration time is almost 30-45 minutes and is approximately 27 µg/ml. When administered intravenously 0.75 g and 1.5 g at the end of the infusion, the maximum concentration is 50 µg/ml and 100 µg/ml, respectively.

The plasma protein binding is from 33% to 50%. Therapeutic concentrations are observed in pleural and synovial fluids, bile, sputum, bone tissue, cerebrospinal fluid (in meningitis), myocardium, skin and soft tissues. Passes through the placenta, is excreted in breast milk, penetrates the blood-brain barrier in meningitis.

Approximately 85–90% of the dose is excreted unchanged by the kidneys after 24 hours (50% is excreted in the renal tubules, 50% is filtered in the glomeruli).

The half-life of intravenous and intramuscular injections is approximately 70 minutes (in newborns it can be 3-5 times longer).

Clinical particulars.

Therapeutic indications.

Treatment of infections caused by cefuroxime-susceptible microorganisms, or treatment of infections before identifying the causative agent of an infectious disease.

Respiratory tract infections: acute and chronic bronchitis, infected bronchiectasis, bacterial pneumonia, lung abscess, postoperative chest infections;

infectious diseases of the throat, nose: sinusitis, tonsillitis, pharyngitis;

urinary tract infections: acute and chronic pyelonephritis, cystitis, asymptomatic bacteriuria;

soft tissue infections: cellulite, erysipeloid, wound infections;

infectious diseases of bones and joints: osteomyelitis, septic arthritis;

infections in obstetrics and gynecology: infectious and inflammatory diseases of the pelvic organs; gonorrhea, especially in cases when penicillin is contraindicated;

other infectious diseases, including septicemia and meningitis.

Prevention of infectious complications after operations on the chest and abdomen, pelvic organs, vascular, cardiovascular and orthopedic operations.

Cefuroxime monotherapy is effective in most cases but can be used in combination with aminoglycoside antibiotics or metronidazole (orally, in suppositories or by injection) if needed.

In the case of presentor expected mixed aerobic and anaerobic infection (e. g peritonitis, aspiration pneumonia, lung, pelvic and brain abscess) and a high probability of such infection (e. g in colon surgery and gynecological surgery), the use of cefuroxime in combination with metronidazole is acceptable.

In the treatment of pneumonia and exacerbation of chronic bronchitis, the medicinal product can be prescribed before oral administration of cefuroxime axetil, when necessary.

Contraindications.

Hypersensitivity to cefuroxime or to other components of the medicinal product.

Hypersensitivity to cephalosporin antibiotics.

Presence of a history of severe hypersensitivity (anaphylactic reactions) to other β-lactam antibiotics (penicillins, monobactams and carbapenems).

Interaction with other medicinal products and other forms of interaction

Medicinal products that reduce platelet aggregation (nonsteroidal anti-inflammatory drugs, salicylates, sulfinpyrazone) - cefuroxime, inhibiting the gut flora, interferes the synthesis of vitamin K, as a result - increases the risk of bleeding.

Anticoagulants – increase of anticoagulant action, as a result - increases the risk of bleeding. Concomitant use with oral anticoagulants may lead to an increase in the International Normalized Ratio (INR).

Diuretics and potentially nephrotoxic antibiotics (e.g., aminoglycosides) - increases the risk of nephrotoxic effects. High-dose cephalosporin antibiotics should be used with caution in patients

receiving potent diuretics (such as furosemide) or potential nephrotoxic medicinal products (such as aminoglycoside antibiotics), as renal impairment cannot be ruled out with this combination. In combination with aminoglycoside antibiotics there is an additive effect, in some cases there is a synergism.

Probenecid. Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended because it reduces tubular secretion and reduces the renal clearance of cefuroxime, which leads to an increase of its concentration in the serum.

Oral contraceptives - cefuroxime inhibits the gut microflora, thereby reducing the reabsorption of estrogen from the intestine, resulting in reduced effectiveness of combined oral contraceptives.

Interference with diagnostic tests.

During treatment with cefuroxime, blood and plasma glucose levels are recommended to be determined by glucose oxidase or hexose kinase methods, as a false negative result may occur in the ferrocyanide test (see section "Special warnings and precautions for use").

Cefuroxime does not affect the results of enzymatic methods for the determination of glucosuria.

Cefuroxime may have little effect on the use of copper reduction methods (Benedict's, Fehling's, Clinitest), but this does not lead to pseudo-positive results, as is the case with some other cephalosporins.

Cefuroxime does not affect the results of alkaline picrate creatinine levels.

The development of a positive Coombs test during treatment with cefuroxime may affect the determination of blood group due to the property of cephalosporins to be absorbed on the surface of the red blood cell membrane and their interaction with antibodies (see section "Undesirable effects").

Special warnings and precautions for use.

The medicinal product should be used with caution in newborns, premature infants, patients with severe renal impairment, colitis, decreased blood clotting, gastric and duodenal ulcers, the elderly, patients with renal insufficiency.

Hypersensitivity reactions.

As with other β -lactam antibiotics, severe and sometimes fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of β -lactam agent. The medicinal product should be used with caution in patients with a history of hypersensitivity reactions to other β -lactam antibiotics.

Concurrent treatment with potent diuretics or aminoglycosides.

With long-term use, it is recommended to monitor renal function in the elderly and patients with known pre-existing renal impairment (especially at high doses) and to prevent dysbacteriosis. High-dose cephalosporin antibiotics should be used with caution in patients receiving concomitant treatment with potent diuretics such as furosemide or aminoglycoside antibiotics, as there have been reports of adverse effects on renal function in this combination. In patients with impaired renal function, the dose should be reduced taking into account the severity of renal failure and susceptibility of the pathogen. Renal function should be monitored in these patients as well as in elderly patients and in patients with pre-existing renal insufficiency (see section "Posology and method of administration").

Growth of non-susceptible microorganisms.

As with other antibiotics, prolonged use of cefuroxime may lead to overgrowth of non-susceptible microorganisms (e. g. *Candida*, *Enterococci*, *Clostridium difficile*), which may require discontinuation of treatment (see section "Undesirable effects").

Cases of pseudomembranous colitis of varying severity have been reported with the use of antibiotics: from easy to life-threatening. Therefore, it is important to consider this diagnosis in patients who develop diarrhea during or after antibiotic use (see section "Undesirable effects"). In the event of protracted and significant diarrhea, or if the patient having abdominal spasms, discontinuation of therapy with cefuroxime and the administration of specific treatment for

Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Intra-abdominal infections.

Due to its spectrum of activity, cefuroxime is not suitable for the treatment of infections caused by gram-negative non-fermenting bacteria.

Intracameral use and ocular disorders.

Cefuroxime is not formulated for intracameral use. Individual cases of serious ocular undesirable effects have been reported following irrational intravenous administration of cefuroxime sodium approved for intravenous/intramuscular administration. These reactions included macular edema, retinal edema, retinal detachment, retinal toxicity, visual impairment, decreased visual acuity, blurred vision, corneal opacity, and corneal edema.

Other relevant information

After elimination of symptoms of a disease treatment should be continued within 48-72 hours.

As with other meningitis regimens, moderate to severe hearing loss has been reported in several patients treated with cefuroxime.

As with other antibiotics, a culture of *Haemophilus influenzae* is detected in the cerebrospinal fluid 18-36 hours after cefuroxime injection. However, the clinical significance of this phenomenon is unknown.

When using cefuroxime in sequential therapy, the time of transition to oral administration of cefuroxime is determined by the severity of the infection, the clinical condition of the patient and the susceptibility of the microorganism. The alternation to oral administration is allowed when the general condition of the patient improves. In the absence of clinical improvement within 72 hours, parenteral administration of the medicinal product should be continued. Before using the oral medicinal product should read the instructions for its medical use.

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).

Important information about excipients.

A vial of 0.75 g of cefuroxime contains 42 mg (1.8 mEq) of sodium per vial.

A vial of 1.5 g of cefuroxime contains 84 mg (3.6 mEq) of sodium per vial.

This should be borne in mind in patients on a controlled sodium diet.

Fertility, pregnancy and lactation

Pregnancy.

There are limited data from the use of cefuroxime in pregnant women. Studies in animals do not indicate reproductive toxicity. CEFUROXIM-DARNITSA should be prescribed to pregnant women only if the benefits outweigh the potential risks.

Cefuroxime crosses the placenta and reaches therapeutic levels in amniotic fluid and umbilical cord blood after an intramuscular or intravenous dose to the mother.

Lactation.

Cefuroxime is excreted in breast milk in small quantities. Undesirable effects at therapeutic doses are not expected, but the risk of diarrhea or fungal infection of the mucous membranes in a child cannot be excluded. Therefore, in response to these reactions, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefuroxime therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility.

There are no data on the effect of cefuroxime sodium on fertility in humans. Animal reproductive studies have shown no effect of this medicinal product on fertility.

Effects on ability to drive and use machines

No studies on the effects of cefuroxime on the ability to drive and use machines have been performed. However, given the known undesirable effects, it can be concluded that cefuroxime is unlikely to affect the rate of reaction when driving or operating machinery.

Posology and method of administration.

Sensitivity to cefuroxime varies from region to region and may change over time. If necessary, refer to local data on antibiotic susceptibility.

The medicinal product should be administered only intramuscularly and intravenously.

Because cefuroxime is also available in an oral form, it is possible to switch sequentially from parenteral therapy to oral therapy where clinically appropriate.

Solvents for cefuroxime powder: 5% glucose solution for injection, 10% glucose solution for injection, 0.9% sodium chloride solution for injection, 5% glucose solution with 0.9% or 0.45%, or 0.225% sodium solution chloride for injection, Ringer's solutions, Ringer's lactate, Hartmann's, water for injections.

Intramuscularly: add 3 ml of water for injections to 0.75 g of the medicinal product, shake the vial gently to form a homogeneous suspension.

Intravenously: Dissolve 0.75 g of the medicinal product in at least 6 ml of water for injections, 1.5 g in 15 ml of solvent in a 20 ml syringe, shake gently until completely dissolved.

For short-term intravenous infusions (up to 30 minutes): Dissolve 0.75 g of the medicinal product in at least 25 ml of solvent (water for injections, 0.9% sodium chloride solution, 5% glucose solution), 1.5 g in 50-100 ml of solvent.

Solvents for intravenous administration: 5% glucose solution for injection, 5% glucose solution and lactated Ringer's solution for injection, 5% glucose solution and 0.9% sodium chloride solution for injection, 10% glucose solution for injection, lactated Ringer's solution for injection, 0.9% sodium chloride solution for injection. The resulting solutions can be injected directly into a vein or into a drip tube during infusion therapy. During storage of ready-made solutions, color saturation changes may occur.

Adults should be given 0.75 g of the medicinal product 3 times a day intramuscularly or intravenously, and 1.5 g 3 times a day intravenously for more severe infections. If necessary, the interval between injections can be reduced to 6 hours. The daily dose of the medicinal product is 3-6 g. If necessary, some infections can be treated according to the following scheme: 750 mg or 1.5 g twice daily (intravenously or intramuscularly) followed by oral cefuroxime.

Infants and children should be prescribed at a dose of 30-100 mg/kg per day for 3-4 injections. For most infections, the optimal daily dose is 60 mg/kg per day.

Newborns should be prescribed 30-100 mg/kg per day for 2-3 injections. It should be considered that the half-life of cefuroxime in the first weeks of life may be 3-5 times longer than in adults.

In *gonorrhea*, the medicinal product should be administered in a dose of 1.5 g once in one or two injections of 0.75 g, which should be injected into both buttocks.

With *meningitis*: used as monotherapy in bacterial meningitis if it is caused by susceptible strains.

Adults should be prescribed 3 g intravenously every 8 hours; *infants, children* to appoint 200-240 mg/kg per day intravenously for 3-4 injections. This dosage can be reduced to 100 mg/kg per day intravenously after 3 days of use or with clinical improvement. *Newborns* should be prescribed the medicinal product at a dose of 100 mg/kg per day intravenously. The dose may be reduced to 50 mg/kg per day in case of clinical improvement.

Prophylaxis

For the prophylaxis of infections *in abdominal, pelvic and orthopedic operations*, the medicinal product is administered intravenously at an average dose of 1.5 g during anesthesia. If necessary, additional intramuscular administration of 0.75 g 3 times a day for the next 24-48 hours is possible.

For *operations on the heart, lungs, esophagus and blood vessels*, the usual dose is 1.5 g intravenously, the medicinal product is administered at the stage of induction of anesthesia, then supplemented by intramuscular injection at a dose of 0.75 g 3 times a day for the next 24-48 hours.

In case of total joint replacement, 1.5 g of the medicinal product is mixed with one package of methyl methacrylate cement-polymer before adding the liquid monomer.

Sequential therapy.

Pneumonia: 1.5 g of the medicinal product 2-3 times a day (intramuscularly or intravenously) for 48-72 hours, followed by switching to the oral form of cefuroxime 500 mg 2 times a day for 7-10 days.

Exacerbation of chronic bronchitis: 0.75 g of the medicinal product 2-3 times a day (intramuscularly or intravenously) for 48-72 hours, followed by switching to the oral form of cefuroxime 500 mg 2 times a day for 7 days.

The duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical condition of the patient.

Renal function impairment.

Cefuroxime is excreted by the kidneys. Therefore, as with other similar antibiotics, it is recommended that patients with impaired renal function reduce the dose of cefuroxime to compensate for the slower excretion of the medicinal product. There is no need to reduce the standard dose (750 mg - 1.5 g 3 times a day) if the creatinine clearance is more than 20 ml/min. Adults with severe renal impairment (creatinine clearance 10-20 ml/min) are recommended a dose of 750 mg 2 times a day, in more severe cases (creatinine clearance less than 10 ml/min) - 750 mg 1 time per day.

For hemodialysis, 750 mg should be administered intravenously or intramuscularly at the end of each dialysis session. In addition to parenteral administration, cefuroxime can be added to peritoneal dialysis fluid (usually 250 mg for every 2 liters of dialysis fluid). For patients on programmed hemodialysis or high-flow hemofiltration in intensive care units, the recommended dose is 750 mg twice daily. Patients undergoing low-flow hemofiltration should follow a dosing schedule for the treatment of renal impairment.

Children.

Medicinal product is used for children from the first days of life. The safety profile of cefuroxime in children corresponds to a similar profile in adult patients.

Overdose.

An overdose of cephalosporins can lead to the development of symptoms of brain irritation, which can lead to convulsions, encephalopathy and coma.

Symptoms of overdose may occur if the dose is not reduced accordingly in patients with impaired renal function (see sections "Posology and method of administration" and "Special warnings and precautions for use").

Treatment. The use of anticonvulsants, respiratory protection, ventilation and perfusion, control and maintenance at the required level of vital indicators, blood gases and electrolytes, hemo- and peritoneal dialysis.

Undesirable effects.

The most common undesirable effects are neutropenia, eosinophilia, transient elevations in liver enzymes or bilirubin, especially in patients with pre-existing liver disease, but no evidence of hepatic impairment or injection site reactions.

The incidence of undesirable effects below is approximate, as for most reactions there are insufficient data for such a calculation. In addition, the incidence of undesirable effects associated with the use of cefuroxime varies depending on the indications.

Clinical trial data were used to rank undesirable effects from very common to very rare. Undesirable effects are predominantly very rare (less than 1/10 000) and generally mild and reversible in nature and are mainly based on post-marketing experience and reflect a higher incidence of adverse reactions than an incidence. In addition, the incidence of undesirable effects varies depending on the indications and is listed below by organ system classes, frequency and severity according to the MedDRA classification.

Adverse events have been ranked under headings of frequency using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10\ 000$).

Ear and labyrinth disorders: very rare - in the treatment of meningitis in children loss of moderate and mild severity have been observed.

Gastrointestinal disorders: Uncommon - discomfort in the digestive tract, abdominal pain, nausea, vomiting, diarrhea; frequency unknown - cases of pseudomembranous colitis have been described (see section "Special warnings and precautions for use").

Hepatobiliary disorders: Common - transient increase in the activity of liver enzymes (mainly in patients with pre-existing liver pathology, but no data on the harmful effects on the liver); uncommon - transient increase in bilirubin, cholestasis. Transient increase in serum liver enzymes or bilirubin was reversible in nature.

Renal and urinary disorders: frequency unknown - increase in serum creatinine, blood urea nitrogen, decrease in creatinine clearance.

Nervous system disorders: rare - headache, dizziness, convulsions.

Blood and lymphatic system disorders: Common - eosinophilia, neutropenia, decreased hematocrit, decreased hemoglobin; uncommon - leukopenia, Coombs' positive test; frequency unknown - thrombocytopenia, anemia, hemolytic anemia. Cephalosporins have the property of being absorbed on the surface of the red blood cell membrane and interacting with antibodies, causing a positive Coombs' test, which can affect blood grouping and hemolytic anemia.

Immune system disorders: uncommon - hypersensitivity reactions, including skin rash, maculopapular rash, pruritus, urticaria; frequency unknown - drug fever, interstitial nephritis, vascular vasculitis, anaphylaxis, angioneurotic edema, anaphylactic shock.

Skin and subcutaneous tissue disorders: frequency unknown - polymorphic erythema, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Administration site conditions: common - reactions at the injection site, which may include pain, when administered intravenously - a burning sensation at the injection site, thrombophlebitis. Intramuscular pain is more likely to occur at higher doses but is unlikely to lead to discontinuation of treatment.

Infections and invasions: frequency unknown - with long-term use may be overgrowth of non-susceptible microorganisms, such as *Candida*, *Enterococci*, *Clostridium difficile*.

Reported suspected adverse reactions.

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

Shelf life. 2 years.

Special precautions for storage.

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

Incompatibilities.

Cefuroxime should not be mixed in the same syringe with aminoglycoside antibiotics.

The pH of a 2.74% solution of sodium bicarbonate for injection has a significant effect on the color of the solution, so this solution is not recommended for dilution of the medicinal product. However, if necessary, if the patient receives a solution of sodium bicarbonate intravenously by infusion, cefuroxime can be injected directly into the drip tube.

1.5 g of cefuroxime dissolved in 15 ml of water for injections can be used together with an injection of metronidazole (500 mg/100 ml), both medicinal products retain their activity for 24 hours at temperatures below 25 °C.

1.5 g of cefuroxime are compatible with 1 g of azlocillin (in 15 ml of solvent) or with 5 g (in 50 ml of solvent) for 24 hours at a temperature of 4 °C and 6 hours at a temperature of up to 25 °C.

Cefuroxime (5 mg/ml) can be stored for 24 hours at 25 °C in 5% or 10% xylitol solution for injection.

The medicinal product is compatible with solutions containing up to 1% lidocaine hydrochloride.

Cefuroxime is compatible with most commonly used solutions for intravenous injection. It retains its properties for 24 hours at room temperature in the following solutions: 0.9% sodium chloride solution for injection; 5% glucose solution for injection; 0.18% sodium chloride solution with 4% glucose solution for injection; 5% glucose solution with 0.9% sodium chloride solution for injection; 5% glucose solution with 0.45% sodium chloride solution for injection; 5% glucose solution with 0.225% sodium chloride solution for injection; 10% glucose solution for injection;

10% solution of inverted glucose in water for injections; Ringer's solution; lactated Ringer's solution; M/6 sodium lactate solution; Hartmann's solution.

The stability of the medicinal product in 0.9% sodium chloride solution for injection with 5% glucose solution does not change in the presence of hydrocortisone sodium phosphate.

The medicinal product is also compatible for 24 hours at room temperature when diluted in a solution for infusion:

- with heparin (10 or 50 units/ml) in 0.9% sodium chloride solution for injection;
- with a potassium chloride solution (10 or 40 mEq/L) in 0.9% sodium chloride solution for injection.

Nature and contents of container.

1 vial in a pack; 5 vials in a blister; 1 blister in a pack.

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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