

PACKAGE LEAFLET
for medical use of medicinal product

CEFTRIAXONUM-DARNITSA

Qualitative and quantitative composition:

Active substance: ceftriaxone;

1 vial contains: ceftriaxone sodium equivalent to ceftriaxone 0.5 g.

Excipients: absent.

Pharmaceutical form

Powder for solution for injection.

Basic physicochemical properties: almost white or yellowish crystalline powder.

Pharmacotherapeutic group

Antibacterials for systemic use. Other beta-lactam antibacterials. Third-generation cephalosporins. Ceftriaxone. ATC code J01D D04.

Pharmacological properties

Pharmacodynamic properties

Ceftriaxone is the parenteral cephalosporin antibiotic of third-generation with prolonged action.

Microbiology. Bactericidal activity of ceftriaxone is specified by inhibition of cell wall synthesis. Ceftriaxone is active *in vitro* against the majority of gram-negative and gram-positive microorganisms. Ceftriaxone is characterized by very large stability with respect to majority of β -lactamases (both penicillinases, and cephalosporinases) of gram-negative and gram-positive bacteria. Ceftriaxone is active against such microorganisms *in vitro* and in the case of clinical infections (see Section "Indications"):

Gram-positive aerobes. *Staphylococcus aureus* (methicillin- susceptible one), *Staphylococci* coagulase-negative, *Streptococcus pyogenes* (β -haemolytic one of Group A), *Streptococcus agalactiae* (β -haemolytic one of Group B), β -haemolytic streptococci (which do not belong neither to Group F, nor to Group B), *Streptococcus viridans*, *Streptococcus pneumoniae*. Methicillin-resistant *Staphylococcus spp.* is resistant to cephalosporins, including to ceftriaxone. Also, *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria monocytogenes* show resistance to ceftriaxone.

Gram-negative aerobes. *Acinetobacter lwoffii*, *Acinetobacter anitratus* (mainly, *A. baumannii*)*, *Aeromonas hydrophila*, *Alcaligenes faecalis*, *Alcaligenes odorans*, *Alcaligenes*-like bacteria, *Borrelia burgdorferi*, *Capnocytophaga spp.*, *Citrobacter diversus* (including *C. amalonaticus*), *Citrobacter freundii**, *Escherichia coli*, *Enterobacter aerogenes**, *Enterobacter cloacae**, *Enterobacter spp.* (other ones)*, *Haemophilus ducreyi*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Hafnia alvei*, *Klebsiella oxytoca*, *Klebsiella pneumoniae***, *Moraxella catarrhalis* (earlier named as *Branhamella catarrhalis*), *Moraxella osloensis*, *Moraxella spp.* (other ones), *Morganella morganii*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Plesiomonas shigelloides*, *Proteus mirabilis*, *Proteus penneri**, *Proteus vulgaris**, *Pseudomonas fluorescens**, *Pseudomonas spp.* (other ones)*, *Providentia rettgeri**, *Providentia spp.* (other ones), *Salmonella typhi*, *Salmonella spp.* (non-typhoid ones), *Serratia marcescens**, *Serratia spp.* (other ones)*, *Shigella spp.*, *Vibrio spp.*, *Yersinia enterocolitica*, *Yersinia spp.* (other ones).

* Some isolates of these species are resistant to ceftriaxone, mainly, due to production of chromosomally encoded β -lactamases.

** Some isolates of these species are resistant to ceftriaxone due to production of range of plasmid mediated β -lactamases.

Note. Many strains of the mentioned above microorganisms that are multiple resistant to such antibiotics like aminopenicillins and ureidopenicillins, cephalosporins of I and II generation,

aminoglycosides are susceptible to ceftriaxone. *Treponema pallidum* is sensitive to ceftriaxone *in vitro* and in animal experiments. Clinical trials show that ceftriaxone is efficient for treatment of the primary and secondary syphilis. With a few exceptions, clinical strains of *P. aeruginosa* are resistant to ceftriaxone.

Anaerobes. *Bacteroides spp.* (bile-sensitive) *, *Clostridium spp.* (excluding the *C. perfringens*), *Fusobacterium nucleatum*, *Fusobacterium spp.* (other), *Gaffkia anaerobica* (former *Peptococcus*), *Peptostreptococcus spp.*

* Some isolates of these species are resistant to ceftriaxone due to β -lactamase-production.

Many strains of β -lactamase-producing *Bacteroides spp.* (notably, *B. fragilis*) are resistant to cephalosporins. *Clostridium difficile* is resistant too.

Susceptibility to ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardised techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued interpretative breakpoints for ceftriaxone are:

Table 1

| | Susceptible | Moderately susceptible | Resistant |
|---|-------------|------------------------|-----------|
| Dilution test inhibitory concentration, mg/l | ≤ 8 | 16-32 | ≥ 64 |
| Diffusion test (disk with 30 μ g of ceftriaxone) inhibition zone diameter, mm | ≥ 21 | 20-14 | ≤ 13 |

Ceftriaxone disk should be used for determination of microorganisms' sensitivity, because *in vitro* tests showed that ceftriaxone is active against certain strains resistant under using of disks intended for all group of cephalosporins.

Instead of NCCLS standard and other well-standardized norms, for example, DIN and ICS, which allow adequate assessment of sensitivity level, can be used for determination of microorganisms' sensitivity.

Pharmacokinetic properties

Pharmacokinetics of ceftriaxone are nonlinear character. All basic pharmacokinetic parameters based on total concentrations of medicinal product depend on dose with the exception of the elimination half-life.

Absorption. The maximum concentration in the blood plasma after a single intramuscular injection of 1 g of the drug is 81 mg/l and is achieved within 2-3 hours after administration. Single intravenous infusions of 1 g and 2 g of the medicinal product after 30 minutes lead to concentrations of 168.1 ± 28.2 and 256.9 ± 16.8 mg/l, respectively. The area under the plasma concentration curve after intravenous administration is equivalent to that after intramuscular administration. This means that the bioavailability of ceftriaxone after intramuscular administration is 100 %.

Distribution. The volume of ceftriaxone distribution amounts is 7-12 l. Ceftriaxone has shown excellent tissue and body fluid penetration after administration a dose of 1-2 g. Over the period of more than 24 hours its concentration well above the minimal inhibitory concentrations against majority of infectious agents for more than 60 tissues and fluids (including lungs, heart, biliary tract, liver, tonsils, middle ear and nasal mucosa, bones as well as cerebrospinal, pleural and synovial fluids, secretion of prostate gland).

After intravenous administration ceftriaxone diffuses rapidly into cerebrospinal fluid, where its bactericidal concentrations against susceptible microorganisms are kept during 24 hours.

Protein binding. Ceftriaxone is reversibly bound to albumin, at that, binding degree is decreased to concentration growth, e.g, it decreases from 95 % under concentration less than 100 mg/l in blood plasma to 85 % under concentration of 300 mg/l. Owing to the low concentration of albumin in tissue fluid the proportion of free ceftriaxone is higher in tissue fluid than in blood plasma.

Penetration into individual tissues. Ceftriaxone penetrates through inflamed meninges of *children*, including, *newborns*. After 24 hours of ceftriaxone administration in dose of 50-100 mg per kg of body mass (newborns and infant respectively) ceftriaxone concentrations in cerebrospinal fluid exceed 1.4 mg/l. The maximal concentration in cerebrospinal fluid is attained approximately in 4 hours after intravenous administration and amounts to 18 mg/l at average. In the case of bacterial meningitis, the average concentration of ceftriaxone in cerebrospinal fluid amounts to 17 % of its concentration in blood plasma, in the case of aseptic meningitis it does to 4 %. In *adult* meningitis patients, administration of the dose in the amount of 50 mg per kg of body mass in 2-24 hour leads to the same concentrations of ceftriaxone in cerebrospinal fluid, that several times exceeds the minimum inhibitory concentrations against the most common causative organisms of meningitis.

Ceftriaxone passes through placental barrier and in low concentrations penetrates into breast milk.

Metabolism. Ceftriaxone is not metabolized systemically; only the intestinal flora transforms the agent into inactive metabolites.

Elimination. The total clearance of ceftriaxone amounts is 10-22 ml/min. Renal clearance amounts is 5-12 ml/min. 50-60 % of ceftriaxone is excreted in interchangeable form through kidneys and its 40-50 % is excreted in interchangeable form together with bile. The elimination half-life of ceftriaxone in adults is amounts nearly 8 hours.

Pharmacokinetics in special classical cases. Kidneys of newborns excrete nearly 70 % of dose. In infants aged less than eight days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 to 3 times that in the young adult group.

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered, and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Therapeutic indications

Indications

Ceftriaxonum-Darnitsa should be used for treatment of infections, which infectious agents are sensitive to ceftriaxone:

- infections of respiratory tracts, especially pneumonia, as well as infections of ear, throat and nose;
- infections of abdominal cavity organs (peritonitis, infection of biliary and gastrointestinal tracts);
- infection of kidneys and urine-excretory tracts;
- infections of genital organs;
- sepsis;
- infections of bones, joints, soft tissues, skin, as well as wound infections;
- infections of patients with impaired immune protection;
- meningitis;
- disseminated Lyme borreliosis (stages II and III).
- It can be used for pre-operative prophylaxis of surgical site infections into organs of gastrointestinal tract, bile-excreting tract, urine-excretory tracts and in the course of gynecological procedures, but only in cases of potential or known contamination.

Upon prescription of medicinal product official recommendations on antibiotic therapy should be observed, and, in particular, recommendations on preventive measures against antibiotic resistance should be kept.

Contraindications

Hypersensitivity to ceftriaxone or to any other cephalosporin. Availability of severe reactions of hypersensitivity (for example, anaphylactic reactions) to any other type of β -lactam antibacterial agents (penicillin's, monobactams and carbapenems) recorded in anamnesis.

Ceftriaxone is contraindicated to:

Premature neonates of age ≤ 41 weeks, taking into consideration terms of prenatal period (gestational age + age after birth). *In vitro* studies showed that ceftriaxone can force out bilirubin from bond with albumin of blood serum, and it results in probable risk of bilirubin encephalopathy in these patients.

Full-term neonates (at the age ≤ 28 days):

- suffer from hyperbilirubinemia, jaundice, hypoalbuminemia or acidosis, because upon such states process of bilirubin binding, probably, is impaired.
- require (or is expected that will require) intravenous administration of calcium-contained medicinal product or infusions of calcium-contained solutions, because there is risk of formation of precipitates of ceftriaxone calcium salt (see Sections “Special warnings and precautions for use” and “Undesirable effects”).

Before intramuscular administration of ceftriaxone, it is necessary to exclude the presence of contraindications to the use of lidocaine, if it is used as a solvent (see section “Peculiarities of Use”). See instructions for use of lidocaine, especially contraindications.

Ceftriaxone solutions that contain lidocaine never should be administered intravenously.

Interaction with other medicinal products and other forms of interaction

Calcium-contained solvents such as the Ringer solution or Gartman solution should not be used for reconstituting of medicinal product in vials or for further dilute a reconstituted solution intended for intravenous administration, because precipitates can be formed. Precipitates of ceftriaxone calcium salt also can be formed upon mixing ceftriaxone with calcium-contained solutions in the same infusion system. Ceftriaxone cannot be administered simultaneously with calcium-contained solutions for intravenous administration, including calcium-contained solutions for long-lasting infusions, such as solutions for parenteral nutrition via a Y-like system. However, in patients other than neonates, ceftriaxone and calcium-contained solutions can be administered sequentially of one another, if the infusion lines are thoroughly flushed between infusions with a compatible fluid. *In vitro* studies, using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone calcium salt (see Sections “Posology and method of administration”, “Contraindications”, “Special warnings and precautions for use”, “Undesirable effects”).

Aminoglycosides. There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases. *Non-steroid anti-inflammatory agents, antiaggregant, and antagonists of vitamin K* (for example, warfarin): increase possibilities of bleeding.

Concomitant use of medicinal product with *oral anticoagulants* may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone (see Section “Undesirable effects”).

Loop diuretic and nephrotic medicinal products increased risk of renal toxicity. No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide).

Bacteriostatic antibiotics (chloramphenicol, tetracycline): decrease bactericidal effect of ceftriaxone. In an *in-vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

Hormonal contraceptives: efficiency of hormonal contraceptives is decreased, therefore, additional (non-hormonal) methods applied for contraception during treatment and over 1 month after its completion are recommended for administration.

Other β -lactam antibiotics: development of crisscross allergic reactions is possible.

No effect similar to that of disulfiram has been demonstrated after ingestion of *ethanol* to immediately administration of ceftriaxone.

Ceftriaxone does not contain N-methylthiotetrazole moiety, associated with possible *ethanol* intolerance and bleeding problems of certain other cephalosporins.

Probenicid: does not influence on tubular secretion of ceftriaxone (unlike with other cephalosporins).

As other antibiotics, ceftriaxone can reduce therapeutic effect of *vaccine against typhus*, however such effect is widespread to attenuated Ty21 strain. Solution Ceftriaxonum-Darnitsa should not be mixed or administered simultaneously with other antimicrobial medicinal products because of their pharmaceutical incompatibility.

Ceftriaxone is not compatible and cannot be mixed with *amsacryne*, *vankomycin*, *fluconazole*, and *aminoglycosides*.

Special warnings and precautions for use

Hypersensitivity reactions

As with all β -lactam antibiotics, cases of serious and occasionally fatal hypersensitivity reactions have been reported (see Section “Undesirable effects”). In case of severe hypersensitivity reactions administration of ceftriaxone must be discontinued immediately, and adequate emergency measures must be initiated. Before beginning treatment, we should ascertain, if the patient anamnesis includes data about his (her) suffering from severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other types of β -lactam agents. Ceftriaxone should be administered carefully for patients, whose anamnesis records non-severe hypersensitivity to other β -lactam medicinal products.

Severe cutaneous adverse reactions (Steven-Johnson syndrome or Lyell’s syndrome/toxic epidermal necrolysis) have been reported; however, the frequency of these phenomena is not known (see Section “Undesirable effects”).

Interaction with calcium containing medicinal products

With respect to prematurely born and full-term newborns at the age of 1 month there are described cases of formation of precipitates of ceftriaxone calcium salt in their lungs and kidneys with fatal outcome. At least one of these patients was treated by administration of ceftriaxone and calcium in different hours, using different intravenous systems. According to available scientific data confirmed cases of formation of intravascular precipitates with the exception of newborns, which were treated with ceftriaxone and calcium-contained solutions or with any other calcium-contained medicinal products, were not registered. Examinations *in vitro* showed that newborns are threatened with increased risk of formation of ceftriaxone calcium salt precipitates in comparison with patients of other age-related groups.

Upon administration of ceftriaxone for treating patients of any age this medicinal product cannot be mixed or administered simultaneously with any calcium-contained solutions for intravenous administration even upon using of various infusion systems or upon administration of medicinal products into various body areas. However, patients older than 28 days can be treated with ceftriaxone and calcium-contained solutions successively and one-by-one provided that medicinal products are administered through various infusion systems into various parts of body or with the aid of exchange of the used infusion system for physiological salt solution made between administrations of these preparations for preventing precipitate formation. Medical employees can prescribe alternative antibacterial agents, which administration is not connected with the similar risk of precipitate formation for patients, who are in need of permanent infusion of calcium-contained solutions for full parenteral nutrition (FPF). If administration of ceftriaxone for patients, who are in need of permanent nutrition, is recognized to be necessary, then solutions for FPF and ceftriaxone can be administered simultaneously, although with using of different infusion systems and of various parts of body. Also, introduction of solutions for FPF can be discontinued for time of ceftriaxone infusion and wash infusion systems within the period between administrations of solutions (see Sections “Contraindications”, “Undesirable effects” and “Incompatibilities”).

Children

Safety and efficiency of ceftriaxone for newborns, infants and children were ascertained for doses described in Section “Posology and method of administration”. Examinations showed that ceftriaxone as some other cephalosporins can exclude bilirubin from bond with albumin of blood serum.

This medicinal product is contraindicated to prematurely born and full-term newborns, who are threatened with risk of kernicterus development (see Section “Contraindications”).

Immune mediated hemolytic anemia

Cases of immune-mediated hemolytic anemia were observed among patients whom antibacterial agents of Cephalosporins’ class were administered (see Section “Undesirable effects”). Severe cases of hemolytic anemia including ones with fatal outcome were recorded both among adults and children within the period of the ceftriaxone treatment.

If in the course of the ceftriaxone treatment anemia is arisen in patient, then the diagnosis of anemia associated with cephalosporin administration should be considered and ceftriaxone administration should be discontinued till ascertaining causation of decease.

Long term treatment

Upon long-term treatment the complete blood count should be conducted on a regular basis. Ceftriaxone can increase the prothrombin time. In connection with it upon suspecting deficit of vitamin K the prothrombin time should be defined.

Colitis/overgrowth of non-susceptible microorganisms

Cases of colitis and pseudomembranous colitis associated with administration of antibacterial agents were recorded on the background of administration of almost all antibacterial agents including ceftriaxone. Severity of these decreases can vary from easy to life-threatening one. Therefore, it is important to take into consideration probability of such diagnosis with respect to patients, who began to suffer from diarrhea during or after the ceftriaxone administration (see Section “Undesirable effects”). It is worth thinking to discontinue the ceftriaxone therapy and administrate proper medical agents against *Clostridium difficile*. Medicinal products that suppress peristalsis should be not administered.

As and upon administering other antibacterial agents, super-infections caused by microorganisms insensitive to the administered medical agent can arise (enterococcus and *Candida* strains).

Ceftriaxone should be administered carefully for patients who are suffered from gastrointestinal deceases recorded in their anamnesis, in particular, from colitis.

Severe renal and hepatic insufficiency

The careful clinical monitoring of safety and efficiency of medicinal product is recommended in the case of severe renal and liver impairment (see Section “Posology and method of administration”).

Influence on results of serological testing

Upon the ceftriaxone administration the Coombs test can give false-positive findings. Also, this medicinal product can cause receiving false-positive findings after analysis on the availability of galactosemia (see Section “Undesirable effects”).

False-positive findings can be received upon assessing glucose content in urine with the aid of non-ferment methods. Within the ceftriaxone administration period levels of glucose content in urine should be assessed with the aid of ferment methods of analysis (see Section “Undesirable effects”).

Sodium

Each gram of this medicinal product contains 3.6 millimole of sodium. Patients, who keep diet with sodium content under control, should take it into consideration.

Antibacterial spectrum

Ceftriaxone possesses the limited spectrum of antibacterial activity and can be unfit for administration as mono-therapy agent upon treatment of determined types of infection except cases, when infection agent was already confirmed (see Section “Posology and method of administration”). In cases of polymicrobial infection, when among suspected infection agents are microorganism resistant to ceftriaxone, administration of additional antibiotics should be taken into consideration.

Use of lidocaine

If lidocaine solution is used as a solvent, ceftriaxone can only be administered intramuscularly. Before the introduction of the drug should necessarily take account the contraindications to the use of lidocaine, cautions and other relevant information specified in the instructions for medical use of

lidocaine (see section “Contraindications”). In no case can lidocaine solution be administered intravenously.

Biliary lithiasis

If an ultrasonic image includes shadows, then possibility of precipitates of ceftriaxone calcium salt should be taken into consideration. Shadowing that wrongly considered as gallstones were observed on the ultrasonic image of gallbladder, and the rate of their appearance increased upon the ceftriaxone administration in dose of 1 g/daily and more. The special caution should be observed upon administering this medicinal product for children. Such precipitates vanish after discontinuance of ceftriaxone therapy. In rare cases formation of ceftriaxone calcium salt precipitates is accompanied with symptomatology. If symptoms are available, the conservative non-surgical treatment is recommended, and physician should make decision about withdrawal of administration of this medicinal product grounding on results of benefit-risk assessment for every specific case (see Section “Undesirable effects”).

Biliary stasis

Cases of pancreatitis that probably caused impassability of bile tracts were recorded among patients, who were administered with ceftriaxone (see Section “Undesirable effects”). Majority of such patients were subjected to risk factors of cholestasis development and formation of biliary sludge such as previous substantial therapy, severe decease and total parenteral nutrition. It cannot be excluded that the initiating or additional factor of this disturbance development can be formation of precipitates in bile tracts due to the ceftriaxone administration.

Renal lithiasis

Cases of formation of renal calculuses, which vanished after withdrawal of the ceftriaxone administration, were recorded (see Section “Undesirable effects”). In the case of availability of such symptom’s ultrasound examination should be made. Physician, grounding on results of benefit-risk assessment in every specific case, makes decision about administration of this medicinal product for patients, whose anamnesis includes renal calculuses or hypercalciuria.

The unused medicinal product and/or wastes of the unused medicinal product should be recycled in accordance with demands of normative documents on liquidation of medicinal products.

Fertility, pregnancy and lactation

Pregnancy

Ceftriaxone permeates through the placental barrier. There are limited data on the ceftriaxone administration for pregnant women. Animal studies do not evidence about direct or indirect harmful influence on embryo/fetus, perinatal and postnatal development. Cephalosporins can be administered during pregnancy, especially in the I trimester only, if benefits overweight risks.

Breast feeding

Ceftriaxone permeates into breast milk in low concentrations, but upon administration of this medicinal product in therapeutic doses infants is expected will be not subjected to its influence. However, risk of development of diarrhea and fungous infection of mucous membranes cannot be excluded. Probability of sensitization should be taken into consideration. Decision about discontinuance of breast feeding or refusal from the ceftriaxone administration should be made. It should be made taking into consideration benefits of child breast feeding and ones of this therapy for the woman.

Fertility

Tests of reproductive function have shown no evidence of adverse effect on male or female fertility.

Effects on ability to drive and use machines

Proper tests were not conducted. In connection with possible occurrence of such adverse reactions as dizziness, ceftriaxone can influence on capability to drive motor transport or operate mechanisms.

Posology and method of administration

For adults and children over 12 years of age: 1-2 g of ceftriaxone is prescribed once daily (in every 24 hours). Upon severe infections or upon infections, which agents are only moderately sensitive to ceftriaxone, the daily dose can be increased to 4 g.

Newborns, infants and children under 12 years

Recommended doses for administration of once daily are put forward below.

Newborns under 2 weeks: dose of 20-50 mg per kg of body mass is administered once daily, the daily dose should not exceed 50 mg per kg body mass. There is no difference upon definition of this medicinal product dose for prematurely born and full-term newborns.

Ceftriaxone is contraindicative for newborns ≤ 28 day of age upon necessity (or expected necessity) of treatment with intravenous infusions, which contain calcium, including, for example, parenteral nutrition in connection with risk of formation of precipitates of ceftriaxone calcium salts (see Section "Contraindications").

Newborns and children over 15 days to 12 years: 20-80 mg per kg of body mass is administered once daily.

Adult doses should be prescribed for children with body mass of more than 50 kg.

Intravenous doses of 50 mg/kg or more should be administered by the infusion method during 30 minutes at least.

Middle-aged patients

Dose correction is unnecessary for middle-aged patients.

Treatment duration

Treatment duration depends on indications and clinical course.

Combined therapy

Tests showed that there is synergism between ceftriaxone and aminoglycosides with regard to many gram-negative bacteria. Notwithstanding that increased efficiency of such combinations not always can be provided for, it should be taken into consideration upon availability of severe and life-threatening infections caused by *Pseudomonas aeruginosa*. Due to physical incompatibility of ceftriaxone and aminoglycosides they should be administered individually in recommended doses.

Dosing in special cases

Meningitis

If newborns and children over 15 days to 12 years old suffer from bacterial meningitis, then treatment should be begun from dose of 100 mg/kg (but not more than 4 g in total) administered once daily. As only infection agent will be identified, and its sensitivity will be identified, the dose can be properly reduced. Best results can be achieved upon such treatment duration:

Table 2

| | |
|---------------------------------|--------|
| <i>Neisseria meningitidis</i> | 4 days |
| <i>Hemophilus influenzae</i> | 6 days |
| <i>Streptococcus pneumoniae</i> | 7 days |

Lyme borreliosis: adults and children should be administered 50 mg/kg (the maximal daily dose amounts to 1 g) once daily during 14 days.

Gonorrhea

For the treatment of gonorrhea (caused by strains that form and do not form penicillinase), it is recommended to administer 250 mg as a single intramuscular dose.

Infection prophylaxis in surgery

Administration of the single dose in the amount of 1-2 g of ceftriaxone by 30-90 minutes before operation beginning is recommended for prophylaxis of post-operational infections upon contaminated or potentially contaminated surgical interventions in dependence on infection danger degree. Simultaneous administration of ceftriaxone and one of 5-nitroimidazoles, for example, ornidazole, recommended itself well upon operations on large intestine and on rectum.

Dysfunction of kidneys and liver

The dose should be not reduced for patients with dysfunctions of kidneys, if function of liver remains normal one. Only in the case of kidney impairment of pre-terminal stage (clearance of creatinine amounts to less than 10 ml/minute) the daily dose should not exceed 2 g.

Patient treated by *dialysis* is in no need of additional administration of this medicinal product after dialysis. However, concentration of ceftriaxone in blood serum should be under control, because its rate of excretion can be reduced in these patients. The daily dose of this medicinal product for dialysis-treated patients should not exceed 2 g.

The dose for patients with *liver dysfunctions* should not be decreased if their renal function remains normal one.

Upon *simultaneous severe dysfunction of kidney and liver* concentration of ceftriaxone in blood plasma should be defined on a regular basis and correction of the medicinal product dose should be made if necessary, because excretion level of such patients can be reduced.

Preparation of solutions

Restored solutions should be used at once after preparation.

Intramuscular injection

For intramuscular injection 0,5 g should be diluted in 2 ml of sterile water for injection, injection to do in the center of the big muscle. You should enter no more than 1 g in one area.

~~If lidocaine is used as a solvent, the resulting solution should never be administered intravenously (see section “Contraindications”). For detailed information, you must read the instructions for use of lidocaine.~~

~~The use of lidocaine provides for preliminary testing to determine the individual sensitivity to this drug.~~

Intravenous injection

For intravenous injection 0.5 g of ceftriaxone should be diluted in 5 ml of sterile water for injections administrated by slow intravenous (2-4 minutes).

Intravenous infusion

Intravenous injection should last 30 minutes at least. For preparation of solution for the infusion 2 g of the medicinal product is dissolved in 40 ml of one of following calcium-free infusion liquid: sodium chloride 0.9 %, sodium chloride 0.45 % + glucose 2.5 %, glucose 5 %, glucose 10 %, dextran 6 % in glucose solution of 5 %, hydroxyethyl-starch 6-10 %, and water for injections. Taking into consideration possible incompatibility, ceftriaxone-contained solutions cannot be mixed with solutions that contain other antibiotics both in the course of preparation and in the course of administration.

But 2 g of ceftriaxone and 1 g of ornidazole are physically and chemically compatible in 250 ml of physiological solution of sodium chloride or of glucose solution.

Calcium-contained solvents such as the Ringer solution or Gartman solution cannot be used for dilution of ceftriaxone in bottles or for dilution of restored solution for intravenous administration in connection with probability of formation of precipitates of ceftriaxone calcium salts. Origination of precipitates of ceftriaxone calcium salts also can occur upon mixing ceftriaxone with calcium-contained solutions in one infusion system for intravenous administration. The medicinal product cannot be administered simultaneously with calcium-contained solutions, including long-lasting calcium-contained infusions, for example, parenteral nutrition. However, with exception of newborns ceftriaxone and calcium-contained solutions can be administered successively, if the infusion system is carefully washed-out with the aid of compatible solution within the period between infusions (see Section “Interaction with other medicinal products and other forms of interaction”).

Children

This medicinal product can be administered for children in accordance with dosages mentioned in Section “Posology and method of administration”.

Overdose

Symptoms: nausea, vomiting, diarrhea, fever, leucopenia, thrombocytopenia, Lederer's anemia, skin-related, gastrointestinal and liver reactions, short breath, renal impairment, stomatitis, anorexia, temporal hearing loss, and loss of spatial orientation.

Treatment: conduct the symptomatic and supporting therapy. The specific antidote is absent. Hemodialysis and peritoneal dialysis are not efficient.

Undesirable effects

Ear and labyrinth disorders: vertigo.

Respiratory, thoracic and mediastinal disorders: possible manifestations of hypersensitivity on the part of breath organs, including respiratory impairment, edemas of respiratory tracts, and bronchospasm.

Gastrointestinal disorders: stomatitis, glossitis, loose stool or diarrhea, nausea, vomiting, pancreatitis (possibly caused by obstruction of bile tracts). Such adverse reactions, as a rule, are easy and often vanish during or after treatment discontinuance. Cases of pseudo-membranous colitis and diarrhea after ceftriaxone administration are caused mainly by *Clostridium difficile*.

Majority of these patients faced factors of stagnation risk in bile-excreting tracts, for example, surgical treatment recorded in anamnesis, severe diseases and fully parenteral nutrition.

At that, role of precipitates, formed under influence of ceftriaxone in bile-excreting tracts, cannot be excluded in considering development of pancreatitis.

Hepatobiliary disorders: increasing number of liver ferments in blood serum (AST, ALT, alkaline phosphatase), nuclear icterus. Precipitations of ceftriaxone-calcium salt have been observed in gallbladder (most of all they are observed among patients treated by doses that exceed the recommended standard dose), circulated cholelithiasis of children. Upon intravenous administration of the medicinal product different rate of precipitate formation is observed in children during prospective trials, in some trials it amounts more than 30 %. The rate of precipitate formation is less upon conduction of slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases precipitation is accompanied with such clinical symptoms as pain, nausea and vomit. In these cases, symptomatic treatment is recommended. Precipitation is usually reversible after withdrawal of ceftriaxone administration.

Renal and urinary disorders: oliguria, glycosuria, and hematuria. Precipitates are in kidneys, mainly among children at the age over 3 years, who were treated by high daily doses (80 mg per kg/daily and more) or by general doses of more than 10 g, as well as other factors of risk such as dehydration or immobilization. Precipitation formation in kidneys can run symptom-free or become apparent clinically and is reversible after withdrawal of ceftriaxone administration. In connection with its cases of anuria and dysfunction of kidneys were reported.

Nervous system disorders: headache, vertigo, and cramps. Cases of cramp occurrence upon administration of the drug for small children are reported.

Blood and lymphatic system disorders: neutropenia, leukopenia, granulocytopenia, eosinophilia, thrombocytopenia, anemia (including haemolytic anemia), prolongation of prothrombin time, impaired coagulation, and agranulocytosis. Blood count should be supervised on a regular basis during long-last treatment.

Immune system disorders: reactions of hypersensitivity, including anaphylactic shock, anaphylactic reactions, and anaphylactoid reactions,

Skin and subcutaneous tissue disorders: allergic skin reactions such as hyperemia, skin precipitation, including maculopapular rash, nettle rash, allergic dermatitis, itch, edema, multiform erythema, Stevens-Johnson syndrome, Lyell syndrome/toxic epidermal necrolysis, and acute generalized exanthematous pustulosis.

General disorders and administration site conditions: chill, pyrexia, increased perspiration; hyperemia can be developed, appearance of rash, edema, itch, phlebitis and pain in place of injection after intravenous administration, this effect can be minimized by slow injection lasted at least 2-4 minutes. Intramuscular injection without lidocaine is painful.

Infections: mycosis of genital tracts, possible superinfection caused by yeast, fungi or by other resistant microorganisms located anywhere.

Investigations: rise of creatinine level in blood, the Coombs false-positive test. As other antibiotics, ceftriaxone can cause false-positive result of galactosemia test. False-positive results can be received upon glucose definition in urine, therefore, glucosuria should be defined, if necessary, only by the ferment method in the course of Ceftriaxonum-Darnitsa treatment.

Interaction with calcium: rare cases of severe undesirable effects sometimes with fatal outcome are recorded among premature born and full-term newborns (at the age <28 days), whom ceftriaxone and medicinal products of calcium were administered intravenously. Upon autopsy precipitates of ceftriaxone calcium salt were found in their lungs and kidneys. High risk of precipitates formation among newborns is caused by their small volume of blood and the longer elimination half-life of ceftriaxone compared with the same parameter for adults (see Sections “Contraindications”, “Special warnings and precautions for use”).

There are recorded cases of formation of precipitates in kidneys, mainly among children at the age of 3 years at least, who received large daily doses of medicinal product (for example, ≥ 80 mg per kg/daily) or general doses of more than 10 grams, as well as, who were subjected to additional factors of risk (for example, limited consumption of liquid or bed rest). Risk of formation of precipitates grows among patients deprived of mobility or among patients in dehydration state. Precipitates can be accompanied with symptoms or symptom-free; can result in renal impairment in and anuria and vanished after ceftriaxone administration withdrawal (see Section «Special warnings and precautions for use»).

There are recorded cases of formation of ceftriaxone calcium salt precipitates in gallbladder, mainly among patients, whom this medicinal product was administered in doses exceeding recommended standard ones. According to data of prospective trials among children the rate of precipitates' formation upon intravenous administration of this medicinal product was various; in some trials they amount to more than 30 %. The rate of precipitates' formation obviously is lower upon slow administration of the medicinal product (during 20-30 minutes). Formation of precipitates usually is symptom-free, but in rare cases such clinical symptoms as pain, nausea and vomit were arisen. Symptomatic treatment is recommended in such cases. After ceftriaxone administration withdrawal precipitates usually vanish (see Section “Special warnings and precautions for use”).

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

3 years.

Special precaution for storage

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

Incompatibilities

Ceftriaxonum-Darnitsa cannot be mixed with calcium contained solutions such as Ringer solution and Gartman solution. Also, calcium contained solutions cannot be administered during 48 hours after the last administration of the medicinal product.

Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole, labetalol, and aminoglycosides.

It should be not mixed with other solvents with the exception of those ones listed in Section “Posology and method of administration”.

Nature and contents of container

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

Date of revision of the text

31.10.2019