MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Pharmaceutical Products

TRIXOCEF
Powder for Solution
for Intravenous and Intramuscular Injection
500 mg, 1,000 mg

Stamp: [APPROVED
by the Ministry of Health of the Republic of Belarus
Order of the Ministry of Health of the Republic of Belarus
No. *609* dd. *01.06.2015*]

Trade name Trixocef.
International nonproprietary name Ceftriaxone.
Pharmaceutical form Powder for solution for intravenous and intramuscular injection 500 mg, 1,000 mg.
Appearance Crystal powder from white color to white with yellow and orange tints.
Composition per 1 vial
Ceftriaxone – 500 mg or 1,000 mg
(as ceftriaxone sodium)
Pharmacotherapeutic group Antibacterials for systemic use. Cephalosporins, 3rd generation
ATC Code J01DD04.
Pharmacological properties
Pharmacodynamics
Bactericidal capacity of Trixocef is driven by the inhibition of cell membranes synthesis in microorganisms. Triskotsef acetylates membrane-associated transpeptidases, thus interrupting peptidoglycan cross-linking required for securing durability and rigidity of bacterial cell membrane. Highly resistant to most β-lactamases (both penicillinase and cephalosporinase) produced by gram-positive and gram-negative bacteria. Trixocef is active against *gram-positive aerobes*: Staphylococcus aureus* (methicillin-sensitive strains), Staphylococci coagulase-negative* (methicillin-sensitive strains), Streptococcus pneumoniae, Streptococcus pyogenes (Group A), Streptococcus agalactiae (Group B), Viridans Group Streptococci; *gram-negative aerobes*: Borrelia burgdorferi, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, Providencia spp., Treponema pallidum.
May be resistant *gram-positive aerobes*: Staphylococcus epidermidis**, Staphylococcus haemolyticus**, Staphylococcus hominis**; *gram-negative aerobes*: Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli***, Klebsiella pneumoniae***, Klebsiella oxytoca***, Morganella morganii, Proteus vulgaris, Serratia marcescens; *anaerobes*: Bacteroides spp., Fusobacterium spp., Peptostreptococcus spp., Clostridium perfringes.
Resistant to medication: Enterococcus spp., Listeria monocetogenes, Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Clostridium difficile, Chlamydia spp., Chlamydophila spp., Mycoplasma spp., Legionells spp., Ureaplasma urealyticum.
* Methicillin-sensitive strains are resistant to ceftriaxone; ** resistant in more than 50% cases, at least, in one region; *** ESBL producing strains are always resistant.
Pharmacokinetics
Absorption
After intramuscular administration drug bioavailability equals 100%. After the intramuscular administration the maximum concentration is noted in 2-3 hours, after intravenous

administration it is noted at the end of infusion. Repeated intramuscular or intravenous administration of doses from 500 mg to 2 g every 12-24 hours leads to Trixocef uptake in concentration, which exceeds concentration noted at single administration by 15-36%.

Distribution

Trixocef easily penetrates to body tissues and fluids (including lungs, heart, bile ducts, liver, tonsils, middle ear and nasal mucosa, bones, and also cerebrospinal, pleural and synovial fluids and prostatic secretion).

Trixocef is reversibly bound to albumin, however, the degree of such binding decreases with rising concentration. Due to lesser concentration of albumin in tissue fluid, the share of free Trixocef in it is higher than in plasma.

Trixocef crosses the placental barrier and is excreted with breast milk at low concentrations.

Metabolism

Trixocef is not metabolised systematically, but is converted to inactive metabolites by gut flora.

Elimination

Trixocef total plasma clearance is 10-22 ml/min. Renal clearance equals 5-12 ml/min. 50-60% of Trixocef is excreted unchanged in the urine, and 40-50% is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours.

Pharmacokinetics in particular medical cases

In newborns around 70% of the dose is excreted in the urine. In infants in the first 8 days of life and also in people aged over 75 years the average elimination half-life is two or three times longer than in adults.

In case of renal or hepatic dysfunction, Trixocef pharmacokinetics is altered insignificantly, only slight increase of elimination half-life is noted. If there is only renal dysfunction, elimination in the bile increases, if there is only hepatic dysfunction, elimination in the urine increases.

Indications

Inflammatory infections induced by microorganisms sensitive to the medicine: upper and lower respiratory tract infections (including bacterial meningitis, community-acquired and hospital-acquired pneumonia, lung abscess, pleural empyema, chronic obstructive pulmonary disease); skin and soft tissue infections, infections of bones and joints, intra-abdominal infections, inflammatory infections of pelvic organs and urinary tract (including pyelonephritis), bacterial endocarditis, sepsis, disseminated Lyme borreliosis (early and late stages of disease), infections of ENT organs (including, acute otitis), infections of sex organs (including gonorrhoea and syphilis), and also in case of neutropenic fever and bacteraemia. Postoperative prophylaxis of infections.

Contraindications

Hypersensitivity to ceftriaxone and other cephalosporin, penicillin, monobactam and carbapenems.

Premature neonates up to a postmenstrual age of 41weeks (gestational age + postnatal age), full-term neonates up to 28 days of age with hyperbilirubinaemia, jaundice, hypoalbuminaemia or acidosis, because these conditions may be accompanied by impairment of bilirubin binding with proteins.

In case of intravenous calcium or calcium-containing treatment due to the risk of precipitation of ceftriaxone-calcium salt.

With caution the medicine should be prescribed in case of renal or hepatic dysfunction, enteritis and colitis related to the antibacterial drug administration.

Warnings and precautions

Pregnancy and lactation

Trixocef should not be prescribed *during pregnancy*, except cases when potential benefits for mother outweighs the possible risk for fetus. In each case drug should be taken under the direct medical supervision. If it is necessary to administer Trixocef *during lactation*, discontinuation of breastfeeding should be considered.

Effects on ability to drive and use machines

During treatment with Trixocef, dizziness may occur. In case of such reactions, patients are advised to abstain from driving and from using complex mechanisms during the period of drug administration.

Special warnings

Before beginning treatment it should be established whether a patient has hypersensitivity reactions to ceftriaxone, cephalosporin, penicillin, and other drugs. In case of allergic reaction, treatment should be discontinued and symptomatic treatment should be initiated.

During Trixocef administration both adults and children may suffer immune mediated haemolytic anaemia. If ceftriaxone-induced anaemia is suspected, treatment with Trixocef should be discontinued until causation of disease is determined.

If during Trixocef treatment diarrhea is present, the possibility of pseudo-membranous colitis should be considered.

During Trixocef treatment results of the Coomb's direct test may be positive, which is determined by drug administration.

Trixocef administration may lead to false-positive reaction to glucose in urine. It is advised to use glucose tests based on enzymatic reaction to glucose oxidation.

For patients with *severe hepatic dysfunction* Trixocef concentration in blood plasma should be monitored because such patients may have lower elimination rate.

There is no need to reduce dosage for patients with *renal dysfunction*, if renal function remains normal. Trixocef daily dose should not exceed 2 g only in cases of preterminal renal failure (creatinine clearance less than 10 ml/min).

In cases of combination of *severe renal and hepatic failure* Trixocef concentration in plasma should be regularly determined and, if necessary, the dose should be modified.

Patients on haemodialysis do not require additional drug injection after the session. However, Trixocef concentration in serum should be monitored in view of dose modification because such patients may have lower elimination rate.

During prolonged treatment the state of peripheral blood and indicators of plasma and kidney functionality should be regularly monitored.

In rare cases on gallbladder sonograms shadows may be noted, which disappear after Trixocef discontinuation (even if such fact is followed by pain in right hypochondrium, further antibiotic administration and symptomatic treatment are advised).

Trixocef should not be combined or prescribed together with potassium containing solutions, including solutions for parenteral nutrition containing calcium, such as using various infusion systems due to the risk of insoluble calcium ceftriaxone sodium.

During Triksotserf administration by *senior and fragile patients* vitamin K administration may be required.

Each gram of Trixocef contains 3.6 mmol sodium. This should be taken into consideration in patients on a controlled sodium diet.

Administration and dosage

Trixocef dose and administration are determined depending on sensitivity of the agent, infection severity, and also on the hepato-renal function of the patient.

The drug is injected intramuscularly or intravenously (by stream or drop infusion).

Recommendations on dosage for *adults and children over 12 years of age with the weight over 50 kg:*

*Dose**	*Frequency***	*Indications*
1-2 g	Once daily	Community-acquired pneumonia, chronic obstructive pulmonary disease, intra-abdominal infections, inflammatory infections of pelvic organs and urinary tract (including pyelonephritis)
2 g	Once daily	Hospital-acquired pneumonia, skin and soft tissue infections, infections of bones and joints
2-4 g	Once daily	Neutropenic fever, bacterial endocarditis, bacterial meningitis

* In cases of bacteraemia the maximum recommended dose is advised for administration. ** Twice daily administration (each 12 hours) may be considered where doses greater than 2 g daily are administered.

For the treatment of *acute otitis* a single intramuscular dose of 1-2 g is required. For the treatment of *gonorrhoea* single intramuscular dose of 500 mg is advised. For the treatment of *syphilis* recommended dose equals 500 mg – 1 g once daily (up to 2 g once daily in case of *neurosyphilis*) for 10-14 days, however, in such cases dose recommendations are based on limited data. For the treatment of *disseminated Lyme borreliosis (early and late stages of disease)* recommended dose equals 2 g once daily for 14-21 days. For *pre-operative prophylaxis of surgical site infections* single injection of 2 g prior the operation is advised.

Neonates, infants and children (15 days to 12 years of age) with the weight less than 50 kg the following dosage is advised:

*Dose**	*Frequency***	*Indications*
50-80 mg/kg	Once daily	Intra-abdominal infections, inflammatory infections of pelvic organs and urinary tract (including pyelonephritis), community-acquired and hospital-acquired pneumonia
50-100 mg/kg (max 4 g)	Once daily	Skin and soft tissue infections, infections of bones and joints, neutropenic fever
80-100 mg/kg (max 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max 4 g)		Bacterial endocarditis

* In cases of bacteraemia the maximum recommended dose is advised for administration. ** Twice daily administration (each 12 hours) may be considered where doses greater than 2 g daily are administered.

For the treatment of *acute otitis* a single intramuscular dose of 50 mg/kg is required. For the treatment of *syphilis*, including *neurosyphilis* recommended dose equals 75-100 mg/kg (max 4 g) once daily for 10-14 days, however, in such cases dose recommendations are based on limited data. For the treatment of *disseminated Lyme borreliosis (early and late stages of disease)* recommended dose equals 50-80 mg/kg once daily for 14-21 days. For *pre-operative prophylaxis of surgical site infections* single injection of 50-80 mg/kg prior the operation is advised.

For *children with the weight above 50 kg* adult doses should be given.

For neonates 0-14 days of age the following doses are recommended:

*Dose**	*Frequency***	*Indications*
20-50 mg/kg	Once daily	Intra-abdominal infections, skin and soft tissue infections, inflammatory infections of pelvic organs and urinary tract (including pyelonephritis), community-acquired and hospital-acquired pneumonia, infections of bones and joints, neutropenic fever
50 mg/kg	Once daily	Bacterial endocarditis, Bacterial meningitis

* In cases of bacteraemia the maximum recommended dose is advised for administration. The maximum daily dose equals 50 mg/kg.

Trixocef is contraindicated in premature neonates up to 41 weeks.

For the treatment of *acute otitis* a single intramuscular dose of 50 mg/kg is required. For the treatment of *syphilis*, including *neurosyphilis* recommended dose equals 50 mg/kg once daily for 10-14 days, however, in such cases dose recommendations are based on limited data. For *pre-operative prophylaxis of surgical site infections* single injection of 20-50 mg/kg prior the operation is advised.

Older patients should be treated regular doses with no modifications due to age.

The duration of treatment is determined individually. After the patient becomes afebrile and evidence of bacterial eradication achieved Trixocef administration should be continued for at least 48-72 hours.

Rules for solution preparation and injection

For *intramuscular injection* 500 mg of Trixocef are dissolved in 2 ml, and 1,000 mg – in 3.5 ml of water for injections or 1% lidocaine solution and should be injected deeply into the gluteal muscle. It is advised to inject no more than 1,000 mg into one place.

Lidocaine solution should not be injected intravenously!

For *intravenous injection* 500 mg of Trixocef are dissolved in 5 ml, and 1,000 mg – in 10 ml of water for injections and should be injected within 2-4 min.

For *intravenous infusion* 2 g of Trixocef are dissolved in 40ml of water for injections or one of the following infusion solutions, free of calcium ions: 0.9% sodium chloride, 5% or 10% glucose or 6% dextran. The solution should be administered within 30 min.

Trixocef should not be combined or added to solutions containing other antibiotics or other solvents, except above mentioned because of possible inconsistence.

Standard aseptic rules should be followed at Trixocef dilution.

Side effects

During Trixocef treatment the following side effects were observed, which disappeared themselves or after drug discontinuation:

Digestive disorder: nausea, vomiting, diarhhoea or constipation, loose stool, flatulence, abdominal pain, taste perversion, stomatitis, glossitis, pseudo-membranous enterocolitis, hepatic dysfunction, biliary pseudolithiasis, dysbacteriosis.

Blood and lymphatic system disorder: haemolytic anaemia, leukopenia, leukocytosis, granulocytopenia, haemolytic anaemia, thrombocytopenia, increase of thromboplastin and prothrombin time, eosinophilia.

Allergic reactions: rash, allergic dermatitis, itch, utricaria, oedema, chills, in particular cases – erythema multiforme (Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, toxic epidermal necrolysis (Lyell's syndrome), rarely – serum sickness, anaphylactic and anaphylactoid reactions.

Urinary disorder: rarely – oliguria, haemoturia, glycosuria, serum creatinine increase; in single cases – renal lithiasis, mainly in children over 3 years administering drug in high daily doses (≥ 80 mg/kg/daily) or in the total dose of more than 10 g and also having additional risk factors (including limitation of liquid intake, bed rest). Renal lithiasis is reversible after Trixocef treatment discontinuation.

CNS disorder: rarely – headache, dizziness, convulsion.

Respiratory disorder: hypersensitivity pneumonitis, bronchospasm.

Other: rarely – genital mycosis, vaginitis, body temperature rise, chills, polyhidrosis, blushes, palpitation.

Local reactions: irritation, infiltrate, injection site pain, phlebitis.

Laboratory indicators: Coombs test false-positive, urine glucose determination false positive.

Overdose

Symptoms: nausea, vomiting, diarrhoea.

Treatment: symptomatic. There is no specific antidote. Haemodialysis and dialysis are ineffective.

Interaction with other medicinal products

Trixocef by suppressing intestinal flora prevents synthesis of vitamin K. At simultaneous administration of Trixocef with drugs reducing thrombocyte aggregation (NSAIDs, salicylates, sulfinpyrazone) the risk of bleeding increases. At simultaneous administration with anticoagulants the effect of the latter increases. At simultaneous administration with loop diuretics the risk of renal toxic effect increases.

Trixocef and aminoglycosides are synergetic to many gram-negative bacteria. Trixocef is incompatible with ethanol. Trixocef should not be combined or administered simultaneously with calcium containing solutions, including solutions for parenteral nutrition containing calcium, due to the risk of insoluble calcium ceftriaxone sodium.

Pharmaceutical interaction

Trixocef should not be combined with solutions containing calcium. Trixocef is incompatible with aminoglycosides, thus they should be injected separately in recommended doses.

Storage and shelf life

Keep secured from humidity and light at temperature below 25° C.
Keep out of the reach of children.
Shelf life equals 3 years. Do not use after the expiry of shelf life specified on the package.

How dispensed

Prescription use.

Package

500 mg or 1,000 mg in 10 ml vial.
1 or 5 vials per pack, 24 or 36 vials per box (package for inpatient hospitals).

Manufacturer

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