**INSTRUCTION**
**for medical use**
**of medicinal product**
**LEKFAZOLIN®**

***Composition:***
*active ingredient:* cefazolin;
1 vial contains cefazolin (as cefazolin sodium) − 1.0 g.

**Pharmaceutical form.** Powder for solution for injections.
*Main physical and chemical properties:* powder of white or off-white color.

**Pharmacotherapeutic group.** Antibacterials for systemic use. First-generation cephalosporins.
ATC code J01D B04.

***Pharmacological properties.***
*Pharmacodynamic properties.*
Cefazolin is a semi-synthetic antibiotic of the 1st generation cephalosporin group for parenteral administration. Mechanism of antimicrobial action is due to inhibition of transpeptidase, blockade of mucopeptide biosynthesis in the bacterial cellular wall.
The drug has a wide spectrum of bactericidal action, it is effective against gram-negative and gram-positive microorganisms, including penicillinase-producing and non-producing ones. Its is highly active against the majority of gram-negative microorganisms: *Escherichia coli, Proteus mirabilis, Salmonella spp., Shigella spp., Klebsiella spp.* (including *Klebsiella pneumoniae*), *Enterobacter spp., Haemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Treponema spp., Leptospira spp.* The drug is active against gram-positive microorganisms, in particular *Staphylococcus spp., Streptococcus spp.* (including *Streptococcus pneumoniae*), *Corynebacterium diphtheriae, Bacillus anthracis*.
The majority of indole-positive strains of *Proteus (Proteus vulgaris),* as well as *Enterobacter cloacae, Morganella morganii, Providencia rettgeri, Serratia spp., Pseudomonas spp., Acinetobacter spp.*, and anaerobic cocci *Peptococcus spp., Peptostreptococcus spp.*, including *B. fragilis*, are resistant to cefazolin. The drug has no effect on rickettsia, viruses, fungi, protozoa.
*Pharmacokinetic properties.*
Cefazolin is rapidly absorbed following intramuscular administration, peak plasma concentration of 37-64 μg/mL is achieved in 60 min after injection. Peak drug concentration following intravenous administration of 185 μg/mL is measured immediately after administration. Blood bactericidal concentration is maintained for 8-12 hours. It has good penetration into tissues and body fluids, and the drug is found in therapeutic levels in mucous membranes, sputum, bones, cerebrospinal fluid, penetrates placental barrier and its very low concentrations are excreted into breast milk. 90% of the drug bonds to plasma proteins. It is excreted from the body in urine in unchanged form (about 90%). Low amount of the drug are metabolised in the liver and excreted in bile.
Elimination half-life is about 2 hours after intramuscular administration, 1.8 hours after intravenous administration. If renal function is impaired, elimination half-life is 3-42 hours.

**Clinical particulars.**
***Therapeutic indications.***
Infections due to cefazolin-sensitive microorganisms:
– respiratory tract infections;
– genitourinary infections;
– skin and soft tissue infections;
– infections of bones and joints;
– sepsis;
– endocarditis;

– biliary tract infections.
Prevention of surgical infections.

***Contraindications.***
Hypersensitivity to cephalosporins and other β-lactams.

***Interaction with other medicinal products and other forms of interaction.***
Cefazolin co-administration with the following drugs:
*Probenecid* – slows down excretion of cefazolin leading to its accumulation, prolonged increase in drug levels in the blood;
*anticoagulants* – increases the risk for bleeding;
*aminoglycosides and loop diuretics* (furosemide, ethacrynic acid) – increases the risk of nephrotoxicity; impairment of renal function due to blockade of cefazolin tubular secretion – in this case, drug dose should be reduced and urea nitrogen and creatinine in blood during treatment should be monitored;
*ethanol* – disulfiram-like reactions are possible.
Cefazolin is not recommended concomitantly with antibacterials that have bacteriostatic mechanism of action (tetracycline, sulphanilamides, erythromycin, chloramphenicol).
As with other antibiotics, cefazolin may reduce therapeutic effect of *BCG vaccine, typhoid vaccines*, therefore such combination is not recommended.

***Special warnings and precautions for use.***
Before each new course of treatment with cefazolin, it is required to establish whether the patient has had a history of hypersensitivity reactions to cefazolin, cephalosporins, penicillins, other β-lactams, other medicinal products.
There is a possibility for crossed allergic reactions between penicillins and cephalosporins. Severe hypersensitivity reactions were reported (including anaphylaxis).
Antibiotics should be prescribed with caution in patients with a history of any forms of allergic reactions, especially to medicinal products.
As with other cephalosporins, possibility for severe allergic reactions, including anaphylactic shock cannot be excluded, even if there are no relevant data in a detailed history. Administration of adrenalin (epinephrine), glucocorticoids and other emergency care measures are required in case of such reactions.
Cephalosporins may be absorbed from the surfaces of red blood cell membranes and interact with anti-drug antibodies. This may lead to false positive results of Coombs test (e.g. in children whose mother were exposed to cefazolin), and in very rare cases – to haemolytic anaemia. Cross-reactivity with penicillins may occur in such reaction.
Treatment with antibacterial drugs, especially in case of severe diseases in elderly patients, as well as in weakened patients, children, may lead to antibiotic-associated diarrhoea, colitis, including pseudomembranous colitis. Therefore, if diarrhoea occurs during or after treatment with cefazolin, these diagnoses should be excluded, including pseudomembranous colitis. Cefazolin should be discontinued in case of severe and/or bloody diarrhoea, and appropriate treatment is to be initiated. Toxic megacolon, peritonitis, shock is possible if no treatment is initiated.
The drug should be prescribed with caution in patients with a history of digestive disorders, especially colitis. Prolonged exposure to antibacterials may lead to excessive growth of non-sensitive microorganisms, fungi and development of superinfection, requiring appropriate measures.
Caution is required in patients with impaired renal function, as well as in patients with epilepsy or other central nervous system disorders. Treatment in patients with renal impairment is performed under in-patient settings, daily dose should be reduced in order to avoid toxicity. Dose adjustment for elderly patients with normal renal function is not required.
Intrathecal administration of the drug is not recommended. Severe central nervous system toxicity was reported, including seizures, following such rout of drug administration, as well as in case of drug overdose at the background of renal dysfunction.

Regular monitoring of blood pattern, functional parameters of the liver and kidneys is recommended during prolonged drug exposure.
Prothrombin time should be monitored in patients with impaired synthesis of deficiency of vitamin K (e.g. chronic kidney diseases, in elderly patients, in case of malnutrition, prolonged antibiotic therapy), prolonged administration of anticoagulants before prescription of cefazolin.
False positive results of urine glucose tests performed by non-enzymatic methods are possible during treatment. The drug has no effect on the result of urine glucose tests performed by enzymatic methods.
Only clear freshly prepared drug solutions are suitable for use.

***Pregnancy and lactation.***
Cefazolin is not recommended during pregnancy.
Lactation should be discontinued, if the drug is clearly indicated.

***Effects on ability to drive and use machines.***
Until individual patient's response to the drug is not established, driving and using machines should be avoided, taking into account that such central nervous system disorders as dizziness and seizures may occur during treatment.

***Posology and method of administration.***
Hypersensitivity to antibiotic should be excluded before treatment initiation using skin test.
Cefazolin is administered intramuscularly and intravenously (by drop and stream infusion).
Intrathecal administration is prohibited.
Preparation of solutions for injection and infusion.
*For intramuscular injection*: dissolve content of the vial in 4-5 mL of sterile water for injection or 0.9% sodium chloride solution, vigorously shaking till complete dissolution. Inject deeply into upper external quadrant of gluteus maximus muscle.
*For intravenous stream administration*: dissolve single drug dose in 10 mL of 0.9% sodium chloride solution or sterile water for injection, and inject slowly for 3-5 min.
*For intravenous drop administration*: dissolve 0.5-1 g of the drug in 50-100 mL of water for injection or 0.9% sodium chloride solution, or in one of the following solutions: 5% glucose solution, 10% glucose solution, 5% glucose solution in sodium lactate solution for injections, 0.9% sodium chloride solution with 5% glucose solution for intravenous infusion, 0.45% sodium chloride solution with 5% glucose solution for intravenous infusion, 5% sodium lactate solution or 10% invert sugar solution in water for injection, Ringer solution for injection with or without lactate. Infusion should be performed during 20-30 min (administration rate is 60-80 drops/min). During recovery, vigorously shake vials till complete dissolution. Daily doses for intravenous administration are the same as for intramuscular.
Dosage.
Daily dose of cefazolin for adults is in general 1-4 g, maximal daily dose is 6 g. Single adult dose in case of infections due to gram-positive microorganisms is 0.25-0.5 g every 8 hours. In case of moderate respiratory tract infections due to pneumococci and genitourinary infections, 1 g of the drug is administered every 12 hours. In case of diseases due to gram-negative microorganisms, the drug is administered in the dose of 0.5-1 g every 6-8 hours. In case of severe infectious disorders (sepsis, endocarditis, peritonitis, destructive pneumonia, acute haematological osteomyelitis, complicated urology infections), administer 1-1.5 g with the interval of 6-8 hours.
For prevention of post-operative infectious complications in adults, intramuscular or intravenous administration of cefazolin is recommended:
– in the dose of 1 g 0.5-1 hour before surgical intervention;
– in case of prolonged surgeries (2 hours and more) – additional 0.5-1 g during surgery;
– following surgery – in the dose of 0.5-1 g every 6-8 hours during the first 24 hours.
In some cases (e. g., surgeries on open heart, prosthetic replacement of joints), preventive administration of cefazolin may last for 3-5 days following surgery.

*Children aged from 1 month*: the drug is prescribed in the dose of 20-50 mg/kg daily, diluted for 3-4 administrations, in case of severe infections – 90-100 mg/kg daily is administered (maximal dose). Mean treatment duration is 7-10 days.
*Adult patients with renal impairment*: start with 0.5 g, and then adjust treatment schedule reducing drug dose and increasing intervals between administrations as recommended below.
With clearance of creatinine and serum creatinine concentration, respectively:
– more than 55 mL/min and less than 1.5 mg% – dose adjustment is not required;
– 35-54 mL/min and 1.6-3 mg% – single dose is unchanged, however interval between administrations should be at least 8 hours;
– 11-34 mL/min and 3.1-4.5 mg% – single standard dose should be reduced twice, interval between administrations is 12 hours;
– less than 10 mL/min and more than 4.6 mg% – half of the therapeutic dose is prescribed every 12-18 hours.
*Renal impairment in children*: start with common single dose, then adjust subsequent doses considering the degree of renal failure. Children with moderate renal impairment (clearance of creatinine is 40-70 mL/min), 60% of daily dose is prescribed twice daily every 12 hours; with clearance of creatinine 20-40 mL/min – 25% of daily dose twice daily every 12 hours; in case of severe renal impairment (clearance of creatinine 5-20 mL/min) – 10% of mean daily dose every 24 hours. All recommended doses are started following initial loading dose. Duration of treatment is 7-10 days in average.
*Paediatric population.*
The drug should not be prescribed in children aged under 1 month and premature children.

***Overdose.***
*Symptoms:* dizziness, paraesthesia and headache, possible development of allergic reactions; in patients with chronic renal failure, neurotoxicity is possible with increased readiness to convulsions, generalized seizures, vomiting and tachycardia. Such laboratory deviations are possible: increased creatinine, urea nitrogen, hepatic enzymes and bilirubin, positive results of Coombs test, thrombocytosis/thrombocytopenia, eosinophilia, leukopenia and elongated prothrombin time.
*Treatment:* discontinue drug administration, perform anti-convulsive and desensitizing therapy, if required. In case of severe overdose, maintenance therapy and monitoring of haematological, renal function and blood coagulation system is required till patient's condition becomes stabilized. The drug is excreted via haemodialysis; peritoneal dialysis is less efficient.

***Undesirable effects.***
*Immune system disorders:* rash, itching, skin redness, dermatitis, urticaria, drug-induced fever, angioneurotic oedema, anaphylactic shock, exudative erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, eosinophilia, arthralgia, serum disease, bronchial spasm.
*Blood and lymphatic system disorders:* cases of leukopenia, agranulocytosis, neutropenia, lymphopenia, haemolytic anaemia, aplastic anaemia, thrombocytopenia/thrombocytosis, hypoprotrombinemia, reduced haematocrit, increased prothrombin time, pancytopenia were reported.
*Gastrointestinal disorders:* anorexia, nausea, vomiting, abdominal pain, diarrhoea, flatulence, symptoms of pseudomembranous colitis that may manifest during or after treatment; dysbacteriosis, candidiasis of the digestive tract is possible following prolonged exposure (including candidiasis stomatitis).
*Hepatobiliary system:* isolated cases of transient increase in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, transient hepatitis and cholestatic jaundice, hyperbilirubinaemia.
*Urinary system disorders:* renal impairment (transient increase in urea nitrogen, hypercreatinaemia) without clinical signs of renal failure. Interstitial nephritis and other renal dysfunctions (nephropathy, necrosis of renal pupils, renal failure) were rarely reported.
*Nervous system disorders:* headache, dizziness, paraesthesia, anxiety, agitation, hyperactivity, seizures.

*Administration site conditions:* pain, induration, swelling in the injection site, cases of phlebitis following intravenous administration.
*Other undesirable effects:* general weakness, skin paleness, tachycardia, haemorrhages. Anogenital itching, genital candidiasis and vaginitis is possible in rare cases. Positive results of Coombs test. Superinfection due to drug-susceptible causative agents may develop following prolonged exposure.

***Shelf life.*** 2 years.

**Storage.** Store in original package at temperature not exceeding 25 °C. Keep away from children.

***Incompatibilities.***
It is not recommended to mix cefazolin solution with other medicinal products in one syringe or one infusion system, especially with antibiotics.

**Package.** 1.0 g of powder in vial; 1 vial in the pack.

**Prescription status.** By prescription.

**Manufacturer.** Joint Stock Company «Lekhim-Kharkiv».

**Location.** Ukraine, 61115, Kharkiv region, Kharkiv, Severyna Pototskoho street, building 36.

**Date of the last revision.**