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INSTRUCTION
for medical use of medicinal product
CEFTRIAXONE

Composition:
active ingredient: ceftriaxone;
1 vial contains ceftriaxone (as ceftriaxone sodium) 1.0 g.

Pharmaceutical form. Powder for solution for injections.
Basic physical and chemical properties: White or off-white crystalline powder.

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

Clinical particulars.
Indications.
Ceftriaxone is indicated for the treatment of the following infections when caused by susceptible bacteria:
– respiratory tract infections, especially pneumonia, and ear, throat and nose infections;
– abdominal infections (peritonitis, biliary and gastrointestinal infections);
– renal and urinary infections;
– genital infections, including gonorrhea;
– sepsis;
– bone, joint, soft tissue, skin, and wound infections;
– infection in immune compromised patient;
– meningitis;
– disseminated Lyme borreliosis (stage II and stage III);
Perioperative prevention of infections during surgical interventions on the gastrointestinal tract, bile ducts, urinary tracts and during gynecological procedures, but only in cases of potential or known contamination.
Consideration should be given to official guidelines on the appropriate use of antibacterial agents, in particular, recommendations for the prevention of antibiotic resistance.

Contraindications.
Hypersensitivity to ceftriaxone, to any other cephalosporin. History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).
Ceftriaxone is contraindicated in:
Premature neonates up to a postmenstrual age of ≤41 weeks (gestational age + chronological age)*.
Full-term neonates (up to 28 days of age):
– with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*;
– if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of ceftriaxone-calcium salt (see sections “Special warnings and precautions for use” and “Undesirable effects”).

* *In vitro* studies have shown that Ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.
Contraindications to lidocaine must be excluded before intramuscular injection of Ceftriaxone when lidocaine solution is used as a solvent (see section "Special warnings and precautions for use"). See information in the Instruction for medical use of lidocaine, especially contraindications.
Ceftriaxone solutions containing lidocaine should never be administered intravenously.

Posology and method of administration.
Adults and children over 12 years of age: 1-2 g of Ceftriaxone once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, administered once daily.
Neonates, infants and children up to twelve years
The following dosage schedules are recommended for once daily administration:
Neonates (up to 2 weeks): 20-50 mg/kg bodyweight once daily, not to exceed 50 mg/kg. It is not necessary to differentiate between premature and infants born at term.
Ceftriaxone is contraindicated in neonates (≤28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium (see "Contraindication").
Infants and children (15 days to twelve years): 20-80 mg/kg once daily.
For children with bodyweights of 50 kg or more, the usual adult dosage should be used.
Intravenous doses of 50 mg or more per kg should be given by infusion over at least 30 minutes.
Elderly.
No dose adjustment is required for the elderly.
Duration of treatment.
The duration of therapy varies according to the course of the disease.
Combination therapy.
Synergy between ceftriaxone and aminoglycosides has been demonstrated with many Gram-negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life-threatening infections due to microorganisms such as *Pseudomonas aeruginosa*. Because of physical incompatibility the two medicines must be administered separately at the recommended dosages.
Special dosage instructions.
Meningitis.
In bacterial meningitis in infants and children (15 days to twelve years), treatment begins with doses of 100 mg/kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. Effective results have been found with the following duration of therapy:

Neisseria meningitidis	4 days
Haemophilus influenzae	6 days
Streptococcus pneumoniae	7 days

Lyme borreliosis: adults and children – 50 mg/kg (highest daily dose – 2 g) once daily for 14 days.
Gonorrhea.
For the treatment of gonorrhoea (penicillinase-producing and nonpenicillinase-producing strains), a single IM dose of 250 mg Ceftriaxone is recommended.
Prophylaxis of surgical infections.
To prevent postoperative infections in contaminated or potentially contaminated surgery, the recommended approach – depending on the risk of infection – is a single dose of 1-2 g Ceftriaxone administered 30-90 minutes prior to surgery. In colorectal surgery, concurrent administration of Ceftriaxone with or without a 5-nitroimidazole, e.g. ornidazole, has proven effective.
Renal and hepatic impairment.

In patients with impaired renal function, there is no need to reduce the dosage of Ceftriaxone provided hepatic function is intact. Only in cases of preterminal renal failure (creatinine clearance <10 mL/min) the Ceftriaxone dosage should not exceed 2 g daily.
In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Plasma concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced. A daily dosage of 2 g should not be exceeded in dialyzable patients.
In patients with impaired hepatic function, there is no need to reduce the dosage of Ceftriaxone provided renal function is intact.
In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of Ceftriaxone should be determined at regular intervals and if necessary the dose adjusted as elimination is decreased in these patients.
Preparation of solutions.
As a general rule, the solution should be used immediately after preparation.
The solutions range in colour from pale yellow to amber. This characteristic of the active ingredient is of no significance for the efficacy or tolerance of the drug.
Intramuscular injection.
For IM injection, Ceftriaxone 1 g is dissolved in 3.5 mL of 1% lidocaine solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1 g to be injected at one site.
The lidocaine solution must never be administered intravenously (see “Contraindications”). The information in the Instruction for medical use of lidocaine should be considered.
If lidocaine is used a preliminary allergy test should be performed to determine the individual sensitivity to this drug.
Intravenous injection.
For intravenous injection, Ceftriaxone 1 g is dissolved in 10 mL of water for injections. The intravenous administration should be given slowly over two to four minutes.
Intravenous infusion.
The infusion should last at least 30 minutes. For intravenous infusion, 2 g Ceftriaxone are dissolved in 40 mL of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + glucose 2.5%, glucose 5%, glucose 10%, dextran 6% in glucose 5%, hydroxyethyl starch 6-10% infusions, water for injections. Ceftriaxone solutions should not be mixed with solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.
However 2 g Ceftriaxone and 1 g ornidazole are physically and chemically compatible in 250 ml of either sodium chloride solution or glucose solution.
Diluents containing calcium, (e.g. Ringer’s solution or Hartmann’s solution), should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be co-administered. However, except for newborns, Ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines thoroughly flushed between infusions with compatible solutions (see section “Interaction with other medicinal products and other forms of interaction”).

Undesirable effects.
The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.
The following convention has been used for the classification of frequency: very common, common, uncommon, rare.
Not known (cannot be estimated from the available data). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies; therefore they are referred to the category of reactions of unknown frequency.

Infection and infestations: uncommon: genital fungal infection; rare: pseudo-membranous colitis; uncommon: superinfection.
Blood and lymphatic system disorders: common: eosinophilia, leucopenia, thrombocytopenia; uncommon: granulocytopenia, anaemia, coagulopathy; not known: haemolytic anaemia, agranulocytosis.
Immune system disorders: not known: anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity.
Nervous system disorders: uncommon: sometimes headache, dizziness; not known: seizures.
Ear and labyrinth disorders: not known: vertigo.
Respiratory, thoracic and mediastinal disorders: uncommon: bronchospasm.
Gastrointestinal disorders: common: loose stools, diarrhea; uncommon: nausea, vomiting; not known: pancreatitis, stomatitis, glossitis.
Hepatobiliary disorders: common: hepatic enzymes increased; not known: gall bladder precipitation, kernicterus.
Skin and subcutaneous tissue disorders: common: rash; uncommon: pruritus; rare: urticaria; not known: Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis.
Renal and urinary system disorders: uncommon: haematuria, glycosuria; not known: oliguria, renal precipitation (reversible).
General disorders and administration site conditions: uncommon: phlebitis, injection site pain, pyrexia; rare: oedema, chills.
Laboratory test findings: uncommon: blood creatinine increased; not known: Coombs test false positive, galactosaemia test false positive, non-enzymatic methods for glucose determination false positive.
Infection and infestations.
Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted (see section “Special warnings and precautions for use”).
Ceftriaxone-calcium salt precipitation.
Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged <28 days) who had been treated with intravenous Ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of Ceftriaxone compared with adults (see sections “Contraindications”, “Special warnings and precautions for use”).
Cases of renal precipitation have been reported, primarily in children older than 3 years of age and who have been treated with either high daily doses (e.g. ≥80 mg/kg/day) or total doses exceeding 10 grams and who presented with other risk factors (e.g. fluid restrictions or confinement to bed). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of Ceftriaxone (see section “Special warnings and precautions for use”).
Precipitation of Ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application – above 30% in some studies. The incidence appears to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of Ceftriaxone (see section “Special warnings and precautions for use”).

Overdose.
In overdose Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Specific antidote is not available. Treatment of overdose should be symptomatic.

Use during pregnancy and in nursing women.
Pregnancy.
Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of Ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.
Breast-feeding.
Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of Ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility.
Reproductive studies have shown no evidence of adverse effects on male or female fertility.

Paediatric patients.
This medicinal product can be administered in children using the dosage recommendations mentioned in section “Posology and method of administration”.

Special warnings and precautions for use.
Hypersensitivity reactions.
As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section “Undesirable effects”). In case of severe hypersensitivity reactions, treatment with Ceftriaxone 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 Ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if Ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam age.
Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell’s syndrome/toxic epidermal necrolysis) have been reported; however, the frequency of these events is not known (see section “Undesirable effects”).
Interaction with calcium containing products.
Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates aged less than 1 month have been described. At least one of them had received Ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with Ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that neonates have an increased risk of precipitation of Ceftriaxone-calcium compared to other age groups.
In patients of any age Ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age Ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of Ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and Ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of Ceftriaxone infusion and the infusion lines flushed between solutions (see sections “Contraindications”,

“Undesirable effects” and “Incompatibilities”).
Paediatric patients.
Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described in section “Posology and method of administration”. Studies have shown that Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section “Contraindications”).
Immune mediated haemolytic anaemia.
An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone (see section “Undesirable effects”). Severe cases of haemolytic anaemia, including fatalities, have been reported during Ceftriaxone treatment in both adults and children.
If a patient develops anaemia while on Ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered and Ceftriaxone discontinued until the aetiology is determined.
Long term treatment.
During prolonged treatment complete blood count should be performed at regular intervals.
Colitis/Overgrowth of non-susceptible microorganisms.
Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents, including Ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of Ceftriaxone (see section “Undesirable effects”). Discontinuation of therapy with Ceftriaxone and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.
Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.
Severe renal and hepatic insufficiency.
In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised (see section “Posology and method of administration”).
Interference with serological testing.
Interference with Coombs tests may occur, as Ceftriaxone may lead to false-positive test results. Ceftriaxone can also lead to false-positive test results for galactosaemia (see section “Undesirable effects”).
Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with Ceftriaxone should be done enzymatically (see section “Undesirable effects”).
Sodium.
Each gram of Ceftriaxone contains 3.6 mmol sodium. This should be taken into consideration in patients on a controlled sodium diet.
Antibacterial spectrum.
Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed (see section “Posology and method of administration”). In polymicrobial infections, where suspected pathogens include organisms resistant to Ceftriaxone, administration of an additional antibiotic should be considered.
Use of lidocaine.
In case a lidocaine solution is used as a solvent, Ceftriaxone solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as detailed in the instruction for medical use of lidocaine must be considered before use (see section “Contraindications”). The lidocaine solution should never be administered intravenously.
Biliary lithiasis.
When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at Ceftriaxone

doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of Ceftriaxone therapy. Rarely precipitates of calcium Ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of Ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment (see section “Undesirable effects”).
Biliary stasis.
Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with Ceftriaxone (see section “Undesirable effects”). Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of Ceftriaxone-related biliary precipitation cannot be ruled out.
Renal lithiasis.
Cases of renal lithiasis have been reported, which is reversible upon discontinuation of Ceftriaxone (see section “Undesirable effects”). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.
Disposal of the medicinal product.
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Any expired or unused product should be returned in an original packaging to a supplier (a doctor or a pharmacist) for proper disposal.

Effects on ability to drive and use machines.
Studies have not been performed. Ceftriaxone can cause dizziness. Ceftriaxone can have influence on the ability to drive and use machines.

Interactions with other medicinal products and other forms of interaction.
Calcium-containing diluents, such as Ringer’s solution or Hartmann’s solution, should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, except for newborns, Ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines 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 (see sections “Posology and method of administration”, “Contraindications”, “Special warnings and precautions for use”, “Undesirable effects”).
Concomitant use 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 “Undesirable effects”).
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.
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.
There have been no reports of an interaction between Ceftriaxone and oral calcium-containing products or interaction between intramuscular Ceftriaxone and calcium-containing products (intravenous or oral).
In patients treated with Ceftriaxone, the Coombs' test may lead to false-positive test results.
Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.

Likewise, non-enzymatic methods for glucose determination in urine may yield false-positive results. For this reason, glucose level determination in urine during therapy with Ceftriaxone should be carried out enzymatically.
No impairment of renal function has been observed after concurrent administration of large doses of Ceftriaxone and potent diuretics (e.g. furosemide).
Simultaneous administration of probenecid does not reduce the elimination of Ceftriaxone.

Pharmacological properties.
Pharmacodynamics.
Ceftriaxone is a long acting third generation cephalosporin antibiotic for parenteral administration.
Mechanism of action.
The bactericidal activity of Ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone exerts *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms. Ceftriaxone is highly stable to most beta-lactamases, both penicillinases and cephalosporinases, of Gram-positive and Gram-negative bacteria. Ceftriaxone is usually active against the following microorganisms in vitro and in clinical infections (see "Indications"):
Gram-positive aerobes.
Staphylococcus aureus (methicillin-sensitive), *Staphylococci* coagulase-negative, *Streptococcus pyogenes* (β-hemolytic, group A), *Streptococcus agalactiae (*β-hemolytic, group B), *Streptococci* β-hemolytic (non-group A or B), *Streptococcus viridans, Streptococcus pneumoniae.*
Note. Methicillin-resistant *Staphylococcus* spp. are resistant to cephalosporins, including Ceftriaxone. In general, *Enterococcus faecalis, Enterococcus faecium* and *Listeria monocytogenes* are resistant to Ceftriaxone.
Gram-negative aerobes.
*Acinetobacter lwoffi, Acinetobacter anitratus (*mostly *A. baumanii)*, 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), *Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae**, Moraxella catarrhalis (*former *Branhamella catarrhalis), Moraxella osloensis, Moraxella* spp. (other), *Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Pasteurella multocida, Plesiomonas shigelloides, Proteus penneri*, Proteus mirabilis, Proteus vulgaris, Pseudomonas fluorescens*, Psudomonas* spp. (other)*, *Providentia rettgeri, Providentia* spp. (other), *Salmonella typhi, Salmonella spp.* (*enteritidis* group), *Serratia marcescens, Serratia spp.* (other), *Shigella spp*., *Vibrio* spp., *Yersinia enterocolitica, Yersinia spp*. (other).
*Some isolates of these species are resistant to Ceftriaxone, mainly due to the production of the chromosomally encoded β-lactamase.
**Some isolates of *Klebsiella pneumoniae* are resistant due to production of extended spectrum plasmid mediated β-lactamase.
Note. Many strains of the above microorganisms that are multiple resistant to other antibiotics, e.g. amino- and ureido-penicillins, I and II generation cephalosporins and aminoglycosides, are susceptible to Ceftriaxone. *Treponema pallidum* is sensitive *in vitro* and in animal experiments. Clinical investigations indicate that primary and secondary syphilis respond well to Ceftriaxone therapy. With a few exceptions clinical *P. aeruginosa* isolates are resistant to Ceftriaxone.
Anaerobes.
Bacteroides spp. (bile-sensitive)*, Clostridium spp.* (excluding the *C. perfringens*), *Fusobacterium nucleatum, Fusobacterium spp.* (other), *Gaffkia anaerobica* (former *Peptococcus*), *Peptostreptococci.*
*Some isolates of *Bacteroides spp.* are resistant to Ceftriaxone.
Note. Many strains of β-lactamase-producing *Bacteroides* spp. (notably *B. fragilis)* are resistant to Ceftriaxone. *Clostridium difficile* is resistant.
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:

	Susceptible	Moderately susceptible	Resistant
Dilution test Inhibitory concentrations in mg/L	≤8	16-32	≥64
Diffusion test (disk with 30 µg Ceftriaxone) Inhibition zone diameter in mm	≥21	20-14	≤13

Microorganisms should be tested with the Ceftriaxone disk since it has been shown by *in vitro* tests to be active against certain strains resistant to cephalosporin class disks.
Where NCCLS recommendations are not in daily use, alternative, well standardised, susceptibility interpretative guidelines such as those issued by DIN, ICS and others may be substituted.
Pharmacokinetics.
The pharmacokinetics of Ceftriaxone is non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations (bound and unbound) of Ceftriaxone.
Absorption.
The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2-3 hours after administration. After 30 minutes single intravenous infusions of 1 g and 2 g result in concentrations of 168.1±28.2 and 256.9±16.8 mg/L, respectively. The area under the plasma concentration-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone.
Distribution.
The volume of distribution of Ceftriaxone is 7-12 L. On intravenous administration, Ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.
Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2 g. Concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract, liver, tonsil, middle ear and nasal mucosa, bone; and cerebrospinal, pleural, prostatic and synovial fluids).
Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in the concentration, e.g. from 95% binding at plasma concentrations of <100 mg/L to 85% binding at 300 mg/L. Owing to the lower albumin content, the proportion of free Ceftriaxone in interstitial fluid is correspondingly higher than in plasma.
Ceftriaxone penetrates the inflamed meninges of neonates, infants and children. Peak concentration in CSF is reached about 4 hours after IV injection and gives an average value of 18 mg/L at 50-100 mg/kg. The average extent of diffusion into the cerebrospinal fluid during bacterial meningitis is 17% of the plasma concentration and 4% in patients with aseptic meningitis. Ceftriaxone concentration are >1.4 mg/L in the CSF 24 hours after IV injection of Ceftriaxone in doses of 50-100 mg per kg. In adult meningitis patients, administration of 50 mg/kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common meningitis pathogens.
Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (3-4% of the concentration in the mother’s blood plasma in 4-6 hours).
Metabolism.
Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.
Elimination.

Plasma clearance of total Ceftriaxone is 10-22 ml/min. Renal clearance is 5-12 ml/min. 50-60% of Ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40-50% is excreted unchanged in the bile. The elimination half-life of total Ceftriaxone in adults is about 8 hours.
Pharmacokinetics in special populations.
In neonates, urinary recovery accounts for about 70% of the 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 is 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.

Incompatibilities.
Ceftriaxone should not be added to solutions containing calcium such as Hartmann's solution and Ringer's solution.
Based on literature reports Ceftriaxone is incompatible with amsacrine, vancomycin and fluconazole and aminoglycosides.
Solutions containing Ceftriaxone should not be mixed with other agents except those mentioned in section "Posology and method of administration".

Shelf life. 3 years – package with water for injection 10 ml per ampoule;
2 years – package with lidocaine injection 10 mg/ml, 3.5 ml per ampoule.

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

Package. 1 g of powder in a vial; 1 or 5, or 50 vials in a pack. 1 vial and 1 ampoule with a solvent (lidocaine injection 10 mg/ml, 3.5 ml per ampoule) in a pack. 1 vial and 1 ampoule with a solvent (water for injection 10 ml per ampoule) in a pack.

Prescription status. By prescription.

Manufacturer. Joint Stock Company «Lekhim-Kharkov».
Production from package in bulk manufactured by Qilu Pharmaceutical Co., Ltd., China.

Location. Ukraine, 61115, Kharkov region, Kharkov, Severyna Pototskoho street, building 36.

Date of the last revision.