INSTRUCTION
for medical use of medicinal product
LEKCEF®

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

Pharmaceutical form. Powder for solution for injections.
Main physicochemical properties: white to pale yellow crystalline powder.

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

***Pharmacological properties*.**
Pharmacodynamic properties.
Mechanism of action
Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin-binding proteins. This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.
Resistance
Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:
- Hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases, carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- Reduced affinity of penicillin-binding proteins for ceftriaxone.
- Outer membrane impermeability in Gram-negative bacteria.
- Bacterial efflux pump.

Susceptibility testing breakpoints
Minimum inhibitory concentration breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

	Dilution Test (Minimum inhibitory concentration, mg/l)	
Pathogen	Susceptible	Resistant
Enterobacteriaceae	≤1	>2
Staphylococcus spp.	a.	a.
Streptococcus spp. (groups A, B, C and G)	b.	b.
Streptococcus pneumoniae	≤0.5[c]	>2
Streptococci Viridans group	≤0.5	>0.5
Haemophilus influenzae	≤0.12[c]	>0.12
Moraxella catarrhalis	≤1	>2
Neisseria gonorrhoeae	≤0.12	>0.12
Neisseria meningitidis	≤0.12 [c]	>0.12
Non-species related	≤1[d]	>2

a. Susceptibility inferred from cefoxitin susceptibility.
b. Susceptibility inferred from penicillin susceptibility.
c. Isolates with a minimum inhibitory concentration above the breakpoints are rare. If this is observed, it should be re-tested and, if confirmed, should be sent to a reference laboratory.
d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Susceptible species
Gram-positive aerobes

Staphylococcus aureus (methicillin-susceptible)[£], Staphylococci coagulase-negative (methicillin-susceptible)[£], *Streptococcus pyogenes* (group A), *Streptococcus agalactiae* (group B), *Streptococcus pneumoniae*, *Viridans* group *Streptococci.*

Gram-negative aerobes

Borrelia burgdorferi, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, Providencia spp., Treponema pallidum.

Species that can acquire resistance

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 perfringens.

Resistant microorganisms

Gram-positive aerobes

Enterococcus spp., *Listeria monocytogenes*

Gram-negative aerobes

Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia

Anaerobes

Clostridium difficile

Others:

Chlamydia spp., *Chlamydophila* spp., *Mycoplasma* spp., *Legionella* spp., *Ureaplasma urealyticum*

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

[+] Resistance rates >50% in at least one region.

[%] Extended-spectrum beta-lactamases strains are always resistant.

Pharmacokinetic properties.

Absorption.

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. 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. The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution.

The volume of distribution of ceftriaxone is 7-12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract, liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8-15% increase in mean peak plasma concentration (C_{max}) is seen on repeated administration; steady state is reached in most cases within 48-72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in cerebrospinal fluid in patients with bacterial meningitis are reported to be up to 25% of plasma levels compared to 2% of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in cerebrospinal fluid are reached

approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section Pregnancy and lactation).
Protein binding
Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95% at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85% at a plasma concentration of 300 mg/l).
Biotransformation
Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.
Elimination
Plasma clearance of total ceftriaxone (bound and unbound) 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 ceftriaxone in adults is about 8 hours.
Patients with renal or hepatic impairment
In patients with *renal or hepatic dysfunction*, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two-fold), even in patients with severely impaired renal function.
The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.
In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.
Elderly
In elderly patients aged over 75 years, the average elimination half-life is usually two to three times higher than that of young adults.
Paediatric population
The elimination half-life of ceftriaxone is prolonged in neonates from birth to 14 days of age. The levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.
The plasma clearance and volume of distribution of total ceftriaxone are greater in children than in adults.
Linearity/non-linearity
The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose-dependent and decrease less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.
Pharmacokinetic/pharmacodynamic relationship
As with other beta-lactams, the pharmacokinetic/pharmacodynamic index demonstrating the best correlation with *in vivo* efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration of ceftriaxone for individual target species (i.e. %T > minimum inhibitory concentration).

Clinical particulars.
Therapeutic indications.
Treatment of infections whose pathogens are sensitive to ceftriaxone:
– respiratory tract infections, especially pneumonia, and ear, nose and throat infections;
– intra-abdominal infections (peritonitis, infections of the biliary tract and the gastrointestinal tract);
– renal and urinary tract infections;
– genital infections, including gonorrhoea;
– sepsis;
– infections of bones, joints, soft tissue, skin, and wound infections;

– infections in immunocompromised patients;
– meningitis;
– disseminated Lyme borreliosis (stages II and III).
Perioperative prevention of infections in surgical procedures on the organs of the gastrointestinal tract, biliary tract, urinary tract and gynaecological procedures, but only in cases of potential or known contamination.
When prescribing ceftriaxone, it is necessary to follow the official recommendations for antibiotic therapy and, in particular, recommendations for the prevention of antibiotic resistance.

Contraindications.
Hypersensitivity to ceftriaxone or 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).
Lekcef® is contraindicated in:
– premature neonates ≤41 week taking into account the period of embryofoetal development (gestational age + chronological age)*;
– full-term neonates (≤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 a 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 such 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 Instruction for Medical Use of lidocaine, especially contraindications.
Lekcef® solutions containing lidocaine should never be administered intravenously.

Interaction 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 Lekcef® vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Lekcef® calcium salt precipitates can also be formed when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Lekcef® must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may 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 ceftriaxone calcium salt precipitates (see sections Posology and method of administration, Contraindications, Special warnings and precautions for use, and 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 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).
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.

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 treatment initiation, 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 agents. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.
Severe cutaneous undesirable effects (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 these patients 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, the physician may 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. Also, 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 population.
Safety and effectiveness of Lekcef® in paediatric population have been established for the dosages described under the section Posology and method of administration. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.
Lekcef® is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section Contraindications).
Immune-mediated haemolytic anaemia.
Cases of an immune-mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Lekcef® (see section Undesirable effects). Severe cases of haemolytic anaemia, including fatalities, have been reported during Lekcef® treatment in both adults and children.
If a patient develops anaemia while ceftriaxone administration, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone discontinued until the aetiology is

determined.
Long-term treatment.
During long-term 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 registered with nearly all antibacterial agents, including ceftriaxone. The severity of these diseases may range 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 impairment.
In severe renal and hepatic impairment, close clinical monitoring for safety and efficacy of the medicinal product is advised (see section Posology and method of administration).
Interference with serological testing.
When administering Lekcef®, Coombs test may lead to false-positive test results. Lekcef® 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 Lekcef® should be done enzymatically (see section Undesirable effects).
Sodium.
Each gram of Lekcef® drug contains 3.6 mmol of sodium. This should be taken into consideration in patients on a controlled sodium diet.
Antibacterial activity spectrum.
Lekcef® 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 case of polymicrobial infections, where suspected pathogens include microorganisms resistant to ceftriaxone, administration of an additional antibiotics should be considered.
Use of lidocaine.
In case a lidocaine solution is used as a solvent, ceftriaxone 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 formation of ceftriaxone calcium salt precipitates. 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, ceftriaxone calcium salt precipitates have been associated with symptoms. In symptomatic cases, conservative non-surgical treatment is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment in every concrete case (see section Undesirable effects).
Biliary stasis.
Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with Lekcef® (see section Undesirable effects). Most of such patients presented with risk factors for cholestasis and biliary sludge, such as preceding major therapy, severe illness and total parenteral nutrition. It cannot be excluded that the initiation or additional factor in the development of this disorder may be the formation of precipitates in the biliary tract as a result of the use of Lekcef®.
Renal lithiasis.

Cases of renal lithiasis have been reported, which are 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 in every particular case.
Drug disposal.
Entry of the drug into the environment should be minimized. Disposal of the medicinal product in the sewer system or household waste should be avoided. Any unused medicinal product should be returned to the supplier (doctor or pharmacist) in the original packaging for proper disposal after treatment or expiry date.
Pregnancy and lactation.
Pregnancy.
Ceftriaxone crosses the placental barrier. There are limited amount of data on 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 breast 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.
Effects on ability to drive and use machines.
No relevant studies have been conducted. During treatment with ceftriaxone, undesirable effects may occur such as dizziness, which may influence the ability to drive and use machines.

Posology and method of administration.
Posology
The dose of the medicinal product depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.
The doses recommended for some indications are given below. In particularly severe cases, doses at the higher end of the recommended range should be considered.

Adults and children over 12 years of age (≥50 kg).

Ceftriaxone dosage*	Administration frequency**	Indications
1-2 g	Once daily	Community acquired pneumonia Acute exacerbations of chronic obstructive pulmonary disease Intra-abdominal infections Complicated urinary tract infections (including pyelonephritis)
2 g	Once daily	Hospital acquired pneumonia Complicated skin and soft tissue infections Infections of bones and joints
2-4 g	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection Bacterial endocarditis Bacterial meningitis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for adults and children over 12 years of age (≥50 kg) that require specific dosage schedules.

Acute otitis media

A single intramuscular dose of Lekcef® 1-2 g can be given.

Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, Ceftriaxone may be effective when given as an intramuscular dose of 1-2 g daily for 3 days.

Pre-operative prophylaxis of surgical site infections

2 g as a single pre-operative dose.

Gonorrhoea

500 mg as a single intramuscular dose.

Syphilis

The recommended dose is 500 mg – 1 g once daily increased to 2 g once daily for neurosyphilis for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on limited data. National or local guidance should be taken into consideration as well.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

2 g once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

Paediatric population

Children 15 days to 12 years of age (< 50 kg)

For children with bodyweight of 50 kg or more, the usual adult dosage should be given.

Ceftriaxone dosage*	Administration frequency**	Indications
50-80 mg/kg	Once daily	Intra-abdominal infections Complicated urinary tract infections (including pyelonephritis) Community acquired pneumonia Hospital acquired pneumonia
50-100 mg/kg (max 4 g)	Once daily	Complicated skin and soft tissue infections Infections of bones and joints Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
80-100 mg/kg (max 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max 4 g)	Once daily	Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for children 15 days to 12 years (<50 kg) that require specific dosage schedules

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Lekcef® 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or previous therapy has failed, Lekcef® may be effective when given as an intramuscular dose of 50 mg/kg daily for 3 days.

Pre-operative prophylaxis of surgical site infections

50-80 mg/kg as a single pre-operative dose.

Syphilis

The recommended dose is 75-100 mg/kg (max 4 g) once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration as well.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])
50-80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.
Neonates 0-14 days of age
Lekcef® is contraindicated in premature neonates up to age of 41 weeks including embryofoetal development (gestational age + chronological age).

Ceftriaxone dosage*	Administration frequency	Indications
20-50 mg/kg	Once daily	Intra-abdominal infections Complicated skin and soft tissue infections Complicated urinary tract infections (including pyelonephritis) Community acquired pneumonia Hospital acquired pneumonia Infections of bones and joints Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
50 mg/kg	Once daily	Bacterial meningitis Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should be considered. A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates 0-14 days of age that require specific dosage schedules
Acute otitis media
For initial treatment of acute otitis media, a single intramuscular dose of Lekcef® 50 mg/kg can be given.
Pre-operative prophylaxis of surgical site infections
20-50 mg/kg as a single pre-operative dose.
Syphilis
The recommended dose is 50 mg/kg once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration as well.
Duration of therapy
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48-72 hours after the patient has become afebrile or evidence of bacterial eradication has been achieved.
Elderly
The dosages recommended for adults require no modification in older people provided that renal and hepatic function is satisfactory.
Patients with hepatic impairment
Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.
There are no study data in patients with severe hepatic impairment (see section Pharmacokinetic properties).
Patients with renal impairment
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance less than 10 ml/min), the ceftriaxone dosage should not exceed 2 g daily.
In patients undergoing dialysis, no additional dosing is required following the dialysis. Ceftriaxone is not removed by peritoneal dialysis or haemodialysis. Close clinical monitoring for safety and efficacy of the medicinal product is advised.
Patients with severe hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy of the medicinal product is advised.
Method of administration
Intramuscular administration
Ceftriaxone may be administered by deep intramuscular injection. Intramuscular injection should be injected at the centre of the large muscle. It is recommended to inject not more than 1 g at one site. As the solvent used is lidocaine, the resulting solution should never be administered intravenously (see section Contraindications). The information in the Instruction for Medical Use of lidocaine should be considered.
Intravenous administration
Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy (see section Contraindications and Special warnings and precautions for use). Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.
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 salt (see section Contraindications).
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. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections Contraindications, Special warnings and precautions for use and Incompatibilities).
For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.
Paediatric population.
The drug is used in children according to the dosage given in the section Posology and method of administration.

Overdose.
The drug plasma concentrations cannot be reduced by haemodialysis or peritoneal dialysis. In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. There is no specific antidote. Overdose treatment is symptomatic.

Undesirable effects.
The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.
Data to determine the frequency of ceftriaxone adverse reactions was derived from clinical trials. The frequency of reactions is classified as follows:
very common (≥1/10);
common (≥1/100 <1/10);
uncommon (≥1/1000 <1/100);
rare (≥1/10000 <1/1000);
not known (cannot be estimated from the available data).
Infections and infestations: uncommon – genital fungal infections; rare – pseudomembranous colitis; not known – superinfections.

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 reactions, anaphylactoid reactions, hypersensitivity reactions.
Nervous system disorders: uncommon – headache, dizziness; not known – convulsion.
Ear and labyrinth disorders: not known – vertigo.
Respiratory, thoracic and mediastinal disorders: rare – bronchospasm.
Gastrointestinal disorders: common – diarrhoea, loose stools; uncommon – nausea, vomiting; not known – pancreatitis, stomatitis, glossitis.
Hepatobiliary disorders: common – hepatic enzyme 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: rare – haematuria, glycosuria; not known – oliguria, renal precipitation (reversible).
General disorders and administration site conditions: uncommon – phlebitis, injection site pain, pyrexia; rare – oedema, chills.
Investigations: uncommon – blood creatinine increased; not known – Coombs test false positive, galactosaemia test false positive, non enzymatic methods for glucose determination false positive.
Infections 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, and Pharmacodynamic properties).
Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children over 3 years of age treated with high daily doses (e.g. ≥80 mg/kg/day) or total doses exceeding 10 grams, and who have other risk factors (e.g. dehydration, confinement to bed). The risk of the formation of precipitates increases in immobilized patients or in dehydrated patients. Precipitates may be asymptomatic or symptomatic, and may lead to renal failure and anuria. Precipitates are usually 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 of the drug (20-30 minutes). The formation of precipitates is usually asymptomatic, but in rare cases they have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section Special warnings and precautions for use).

Shelf life. Lekcef®, powder for solution for injections – 3 years.
Lidocaine, solution for injection, 10 mg/ml, 3.5 ml per ampoule – 3 years.
Water for injections, solvent for parenteral administration, 10 ml in ampoule – 4 years.

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

Incompatibilities.
Lekcef® should not be mixed with calcium-containing solutions, such as Ringer's solution or Hartmann's solution because a precipitate can form.
Lekcef® is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides.
It should not be mixed with or added to other agents except those mentioned in section Posology and method of administration. Lekcef® must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition (see section Posology and method of administration, Special warnings and precautions for use and Undesirable effects).

Package. 1.0 g of powder in a vial; 1 or 5, or 50 vials in a pack. 1 vial and 1 ampoule with a solvent (Lidocaine, solution for injection, 10 mg/ml, 3.5 ml per ampoule) in a pack. 1 vial and 1 ampoule with a solvent for parenteral administration (Water for injections, 10 ml in ampoule) in blister, 1 blister 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.