Oricef®

Ceftriaxone USP

Long-acting, broad-spectrum cephalosporin antibiotic for parenteral use

Composition

250 mg i.v. / i.m. injection: Each vial contains Ceftriaxone Sodium USP 298.23 mg equivalent to Ceftriaxone 250 mg.
500 mg i.v. / i.m. injection: Each vial contains Ceftriaxone Sodium USP 596.46 mg equivalent to Ceftriaxone 500 mg.
1 g i.v. / i.m. injection: Each vial contains Ceftriaxone Sodium USP 1.193 g equivalent to Ceftriaxone 1 g.
2 g i.v. infusion: Each vial contains Ceftriaxone Sodium USP 2.386 g equivalent to Ceftriaxone 2 g.
Solvent for parenteral use: The solvent ampoule for i.m. injection contains 1% lidocaine hydrochloride solution, and for i.v. injection sterile water for injections.

Pharmacology

The bactericidal activity of ceftriaxone results from inhibition of bacterial 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 β-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 and usage.):

Gram-positive aerobes:
Staphylococcus aureus (Including penicillancase Producing strains)
Staphylococci epidermis
Streptococcus pneumoniae
Streptococcus group A (Str. pyogenes)
Streptococcus group B (Str. agalactiae)
Streptococcus viridans
Streptococcus bovis

Gram-negative aerobes:
Aeromonas spp.
Alcaligenes spp.
Branhamella catarrhalis (β-lactamase negative and positive)
Citrobacter spp.
Enterobacter spp. (some strains are resistant)
Escherichia coli
Haemophilus ducreyi
Haemophilus influenzae (including penicillinase-producing strains)
Haemophilus parainfluenzae (including penicillinase-producing strains)
Klebsiella spp. (including *Kl. pneumoniae*)
Moraxella spp.
Morganella morganii
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitidis
Plesiomonas shigelloides
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Pseudomonas aeruginosa (some strains are resistant)
Salmonella spp. (including *S. typhi*)
Serratia spp. (including *S. marcescens)*
Shigella spp.
Vibrio spp. (including *V. cholerae*)
Yersinia spp. (including *Y. enterocolitica)*

Note: Many strains of the above microorganisms that are multiple resistant to other antibiotics, e.g. penicillins older 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.

Anaerobic organisms
Bacteroides spp. (including some strains of *B. fragilis*)
Clostridium spp. (except *Cl. difficile*)
Fusobacterium spp. (except *F. mortiferum* and *F. varium*)
Peptococcus spp.
Peptostreptococcus spp.
Note: Many strains of β-lactamase-producing *Bacteroides spp.* (notably *B. fragilis*) are resistant.
Susceptibility to ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardized techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued the following interpretative breakpoints for ceftriaxone:

	Susceptible	Moderately susceptible	Resistant
Dilution test inhibitory concentrations in mg/l	8	16-32	64
Diffusion test (disk with 30 mg 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 standardized susceptibility-interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

Pharmacokinetics

The pharmacokinetics of ceftriaxone are nonlinear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations.

Absorption

The maximum plasma concentration after a single i.m. dose of 1g is about 81 mg/l and is reached in 2-3 hours after administration. The area under the plasma concentration-time curve after i.m. administration is equivalent to that after i.v. administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone.

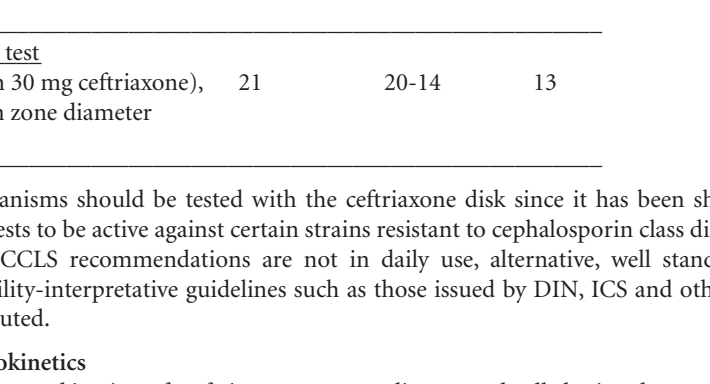
Distribution

The volume of distribution of ceftriaxone is 7-12 l. 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 as well as cerebrospinal, pleural, prostatic and synovial fluids.

On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours (see figure).

Concentration after 1 g ceftriaxone (mg/l)

Protein binding
Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration, e.g. from 95% binding at plasma concentrations of <100 mg/1 to 85% binding at 300 mg/1. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.



Penetration into particular tissues
Ceftriaxone penetrates the inflamed meninges of neonates, infants and children: Ceftriaxone concentrations exceed 1.4 mg/l in the Cerebrospinal Fluid (CSF) 24 hours after i.v. injection of Oricef® in doses of 50-100 mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after i.v. injection and gives an average value of 18 mg/l. Mean CSF levels are 17% of plasma concentrations in patients with bacterial meningitis and 4% in patients with aseptic meningitis.
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.

Metabolism

Ceftriaxone is not metabolized systemically; but is converted to inactive metabolites by the gut flora.

Elimination

50-60% of ceftriaxone is excreted unchanged in the urine, while 40-50% is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours.

Pharmacokinetics in special clinical situations
In neonates, urinary recovery accounts for about 70% of the dose. In infants aged less than 8 days and in elderly persons aged over 75 years the average elimination half-life is usually two to three times that in young adults.
In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Indications & Usage

Infections caused by pathogens sensitive to Oricef®, e.g.:
- sepsis;
- meningitis;
- abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);
- infections of the bones, joints, soft tissue, skin and of wounds;
- infections in patients with impaired defence mechanisms;
- renal and urinary tract infections;
- respiratory tract infections, particularly pneumonia, and ear, nose and throat infections;
- genital infections, including gonorrhoea.

Perioperative prophylaxis of infections.

Dosage and administration

Route of administration: Parenteral
Standard dosage
Adults and children over 12 years: The usual dosage is 1-2 g of Oricef® once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Elderly patients: The dosages recommended for adults require no modification in the case of geriatric patients.

Duration of therapy
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Oricef® should be continued for a minimum of 48-72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination therapy
Synergy between ceftriaxone and aminoglycosides has been demonstrated with many gram-negative bacilli 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 drugs must be administered separately at the recommended dosages.

Special dosage instructions
Meningitis: In bacterial meningitis in infants and children, 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. The best results have been found with the following duration of therapy:

Neisseria meningitidis	4 days
Haemophilus influenzae	6 days
Streptococcus pneumoniae	7 days
Susceptible Enterobacteriaceae	10-14 days

Lyme borreliosis: 50 mg/kg up to a maximum of 2 g in children and adults, once daily for 14 days.

Gonorrhoea(penicillinase-producing and nonpenicillinase-producing strains):
For the treatment, a single i.m. dose of 250 mg Oricef® is recommended.

Perioperative prophylaxis: A single dose of 1-2 g depending on the risk of infection of 30-90 minutes prior to surgery. In colorectal surgery, administration of Oricef® with or without a 5-nitroimidazole, e.g. ornidazole (separate administration, see Method of administration) has been proven effective.

Impaired renal and hepatic function: In patients with impaired renal function, there is no need to reduce the dosage of Oricef® provided hepatic function is intact. Only in cases of preterminal renal failure (creatinine clearance <10 ml/min) should the Oricef® dosage not exceed 2 g daily. In patients with liver damage, there is no need for the dosage to be reduced provided renal function is intact.
In patients with both severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary the dose should be adjusted.
In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Plasma concentrations should , however, be monitored, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

Method of administration

As a general rule the solutions should be used immediately after preparation.
Reconstituted solutions retain their physical and chemical stability for six hours at room temperature (or 24 hours at 5 °C). The solutions range in colour from pale yellow to amber, depending on the concentration and the length of storage. The colouration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection: For i.m. injection, Oricef® 250 mg or 500 mg is dissolved in 2 ml, and Oricef® 1 g in 3.5 ml, of 1% lidocaine hydrochloride solution and administered by deep intragluteal injection. It is recommended that not more than 1 g be injected at one site.
The lidocaine solution must never be administered intravenously.

Intravenous injection: For i.v. injection, Oricef® 250 mg or 500 mg is dissolved in 5 ml & Oricef® 1 g in 10 ml sterile water for injections, and then administered by i.v. injection lasting for 2-4 minutes.
Examine the patients tolerance to ceftriaxone by giving test dose prior to administration.

Intravenous infusion: The infusion should last at least 30 minutes. For i.v. infusion, 2 g Oricef® is dissolved in 40 ml of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, levulose 5%, dextran 6% in dextrose, sterile water for injections. Oricef® solutions should not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Stability

This medicine should not be used after the expiry date (EXP) shown on the pack. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature or 24 hours in the refrigerator at 2-8 °C.

Contraindications

Oricef® is contraindicated in patients with known hypersensitivity to the cephalosporin class of antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.
Although the relevant preclinical investigations revealed neither mutagenic nor teratogenic effects, Oricef® should not be used in pregnancy (particularly in the first trimester) unless absolutely indicated.

Warning and Precautions

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Anaphylactic shock requires immediate countermeasures such as intravenous epinephrine followed by a glucocorticoid.
In rare cases, shadows suggesting sludge have been detected by sonograms of the gallbladder. This condition was reversible on discontinuation or completion of ceftriaxone therapy . Even if such findings are associated with pain, conservative, nonsurgical management is recommended. In-vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Cautions should be exercised when considering Oricef® for hyperbilirubinemic neonates, especially prematures. During prolonged treatment the blood picture should be checked at regular intervals.

Undesirable effects

Oricef® is generally well tolerated. During the use of Oricef®, the following side effects, which were reversible either spontaneously or after withdrawal of the drug, have been observed:

Systemic side effects
Neuropsychiatric symptom such as convulsion.
Gastrointestinal complaints (about 2% of cases) : loose stools or diarrhea, nausea, vomiting, stomatitis and glossitis.
Hematological changes (about 2%): eosinophilia, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia.
Skin reactions (about 1%) : exanthema, allergic dermatitis, pruritus, urticaria, edema, erythema multiforme.
Other, rare side effects: headache and dizziness, increase in liver enzymes, gallbladder sludge, oliguria, increase in serum creatinine, mycosis of the genital tract, shivering and anaphylactic or anaphylactoid reactions.
Pseudomembranous enterocolitis and coagulation disorders have been reported as very rare side effects.

Local side effects
In rare cases, phlebitic reactions occurred after i.v. administration. These may be minimized by slow (two to four minutes) injection.
Intramuscular injection without lidocaine solution is painful.

Use in pregnancy & lactation

Pregnancy Category 'B'. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Use in children & adolescents

Neonates, infants and children up to 12 years: The following dosage schedules are recommended for once daily administration:
Neonates (up to 14 days): A daily dose of 20-50 mg/kg body weight, not to exceed 50 mg/kg, on account of the immaturity of the infant's enzyme systems. It is not necessary to differentiate between premature and term infants.

Infants and children (15 days to 12 years): A daily dose of 20-80 mg/kg.
For children with body weights of 50 kg or more, the usual adult dosage should be used.
Intravenous doses of 50 mg/kg body weight should be given by infusion over at least 30 minutes.

Drug interactions

a) With Medicine: No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide). There is no evidence that Oricef® increases renal toxicity of aminoglycosides. No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of Oricef®. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins. The elimination of Oricef® is not altered by probenecid.

b) With food & others: No

Overdose

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

Storage

Store below 30 °C.

Dosage forms and packs

Oricef® i.m. injection
250 mg i.m. injection: Each vial contains Ceftriaxone Sodium USP 298.23 mg equivalent to Ceftriaxone 250 mg, 1 ampoule containing 2 ml of 1% lidocaine solution and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (5 ml), baby needle, alcohol pad and first aid bandage.

500 mg i.m. injection: Each vial contains Ceftriaxone Sodium USP 596.46 mg equivalent to Ceftriaxone 500 mg, 1 ampoule containing 2 ml of 1% lidocaine solution and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (5 ml), baby needle, alcohol pad and first aid bandage.

1 g i.m. injection: Each vial contains Ceftriaxone Sodium USP 1.193 g equivalent to Ceftriaxone 1 g, 1 ampoule containing 3.5 ml of 1% lidocaine solution and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (5 ml), alcohol pad and first aid bandage.

Oricef® i.v. injection

250 mg i.v. injection: Each vial contains Ceftriaxone Sodium USP 298.23 mg equivalent to Ceftriaxone 250 mg, 1 ampoule containing 5 ml of sterile water for injections and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (5 ml), alcohol pad and first aid bandage.

500 mg i.v. injection: Each vial contains Ceftriaxone Sodium USP 596.46 mg equivalent to Ceftriaxone 500 mg, 1 ampoule containing 5 ml of sterile water for injections and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (5 ml), alcohol pad and first aid bandage.

1 g i.v. injection: Each vial contains Ceftriaxone Sodium USP 1.193 g equivalent to Ceftriaxone 1 g, 1 ampoule containing 10 ml of sterile water for injections and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (10 ml), butterfly needle, alcohol pad and first aid bandage.

Oricef® i.v. infusion

2 g i.v. infusion: Each vial contains Ceftriaxone Sodium USP 2.386 g equivalent to Ceftriaxone 2 g, 1 ampoule containing 20 ml of sterile water for injections and 1 ampoule breaker. It also contains a complementary pouch comprised of sterile disposable syringe (20 ml), butterfly needle, alcohol pad and first aid bandage.

This is a medicament:
-A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
-The doctor and the pharmacist are experts in medicine, its benefits and risks.
-Do not repeat the same prescription without consulting your doctor.

Medicine: Keep out of reach of children

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