Third Generation Cephalosporins

CEFAXONE INJECTION

500mg, 1g

Ceftriaxone sodium

■ **COMPOSITION**: Each vial contains

Ceftriaxone sodium..... 500mg (potency)

..... 1g (potency)

■ **DESCRIPTION**

CEFAXONE INJECTION is a white to pale yellow powder in a colorless transparent vial. Each box comes with 10 vials and a package insert.

■ **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 micro-organisms. Ceftriaxone is highly stable to most ß-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following micro-organisms in vitro and in clinical infections.

Gram-positive aerobes

Staphylococcus aureus (methicillin-sensitive), Staphylococci coagulase-negative, *Streptococcus pyogenes* (ß-hemolytic, group A), *Streptococcus agalactiae* (ß-hemolytic, group B), ß-hemolytic Streptococci (non-group A or B), *Streptococcus viridans, Streptococcus pneumoniae.*

Note: Methicillin-resistant *Staphylococcus* spp. is resistant to cephalosporins, including ceftriaxone. In general, *Enterococcus faecalis, Enterococcus faecium* and *Listeria monocytogenes* are resistant.

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 gonorrhoea, Neisseria meningitidis, Pasteurella multocida, Plesiomonas shigelloides, Proteus mirabilis, Proteus penneri*, Proteus vulgaris*, Pseudomonas fluorescens*, Pseudomonas* spp. (other)*, *Providentia rettgeri*, Providentia* spp. (other), *Salmonella typhi, Salmonella* spp. (non-typhoid), *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 ß-lactamase.

** Some isolates of these species are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase.

Note: Many strains of the above micro-organisms that are multiple resistant to other antibiotics, e.g. amino-penicillins and ureido-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. (bile-sensitive)*, *Clostridium* spp. (excluding C. *difficile*), *Fusobacterium nucleatum, Fusobacterium* spp. (other), *Gaffkia anaerobica* (formerly *Peptococcus*), *Peptostreptococcus* spp.
* Some isolates of these species are resistant to ceftriaxone due to ß-lactamase-production.
Note: Many strains of ß-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant. *Clostridium difficile* is 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 µg ceftriaxone), inhibition zone diameter in mm	≥ 21	20 – 14	≤ 13

Micro-organisms 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 non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing 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.
○ Absorption
Cefaxone is administered as an intramuscular injection or as an IV injection or infusion.

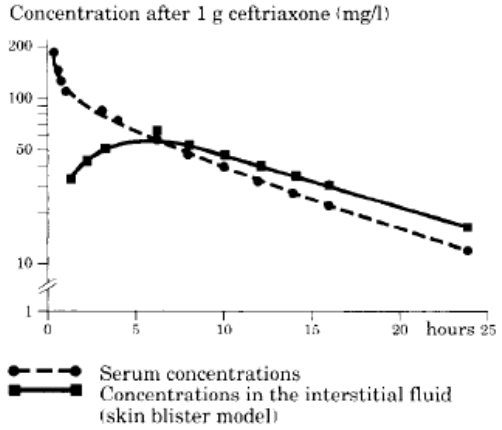
The maximum plasma concentration after a single i.m. dose of 1 g is about 81 mg/l and is reached in 2-3 hours after administration. The area under the plasma concentration-time curve after i.m. administration is equivalent to that after i.v. administration of an equivalent dose, indicating 100% bioavailability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

After intravenous bolus administration of ceftriaxone 500 mg and 1.5 g, mean peak plasma ceftriaxone levels are approximately 151 and 286 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. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose.

- 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).



Protein Binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95% at plasma concentrations below 100mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85% at a plasma concentration of 300mg/l). 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 meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF 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 CSF are reached approximately 4-6 hours after intravenous injection.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

- Metabolism

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

○ Elimination

Total plasma clearance is 10-22 ml/min. Renal clearance is 5-12 ml/min.

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 Populations

Pediatric Population

The 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 neonates, infants and children than in adults.

Geriatric Population

In elderly persons aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Renal Impairment

In patients with renal impairment, the pharmacokinetics of ceftriaxone

are only minimally altered and the elimination half-life is only slightly increased (less than two fold) even in patients with severely impaired renal function.

The 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.

Hepatic Impairment

In patients with hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased (less than two fold).

In this patient population, 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.

■ INDICATIONS

Spectrum of activity

Staphylococcus aureus (including penicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* group A (Str. *Pyogenes*), *Streptococcus* group B (Str. *aggalactiae*), *Streptococcus viridians* group, *Streptococcus bovis, Aeromonas* spp., *Alcaligenes* spp., *Branhamella catarrhalis, Citrobacter* spp., *Enterobacter* spp. (some strains are resistant), *Escherichia coli, Haemophilus ducreyi, Haemophilus influenzae* (including amplicillin-resistant strains) *Haemophilus parainfluenzae, Klebsiella* spp.,(including KI, pneumoniae), *Moraxella* spp., *Proteus morgani, Proteus mirabilis, Proteus vulgaris, Providen-cia* spp., *Neisseria gonorrheae* (including penicillinase producing strains), *Neisseria meningitides, Plesiomonas shigelloides,*

Pseudomonas aeuroginosa (some strains are resistant) *Salmonella* spp. (including *S. typhi), Serratia* spp. (including *S. Marcescens*), *Shigella* spp., *Yersinia* spp. (including *Y. enterocolitica*), *Treponemapallidum*, *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.

INDICATIONS

1. Main Indications

Respiratory tract infections such as pneumonia, bronchitis, etc., ear, nose and throat infections, renal and urinary tract infections, sepsis and meningitis, perioperative prophylaxis of infections, bones and joints infections, infections of skin, wounds and soft tissue, Abdominal infections (peritonitis, infections of biliary and gastrointestinal tract), genital infections such as gonorrhea, etc.

2. Can be used in the following disease: infections in immunosuppressed patients.

■ ADVERSE REACTIONS

1) Shock: As anaphylactic shock may rarely occur cautious monitoring is required, and in case that unpleasantness, stridor, dizziness, tenesmus, tinnitus, sweating, etc. occur further administration should be discontinued and appropriate measures taken.

2) Hypersensitivity: When eruption, urticaria, erythema, reddening, pruritis, chills, fever, allergic, dermatitis, edema, erythema multiforme, anaphylactic or anaphylactoid reaction occur, furthur administration should be discontinued and appropriate measures taken. Severe dermal adverse reaction (erythema multiforme). Steven Johnson syndrome (mucocutaneous-ocular syndrome). Lyell syndrome (toxic epidermal necrolysis) may rarely occur.

3) Blood: Occasionally, agranulocytosis, granulocytopenia, eosinophilia, thrombocytosis, leukopenia, rarely anemia, hemolytic anemia, thrombocytopenia, prothrombin abnormality may occur.

4) Liver: Occasionally elevation of AST, ALT, ALP and symptoms due to precipitation of ceftriaxone calcium salt in the gall-bladder, rarely elevation of bilirubin, y-GTP may occur.

5) Kidney: As severe renal disorder such as acute renal failure has been reported to occur rarely, cautious observation such as periodic monitoring is required and if abnormality is acknowledged, further administration should be discontinued and appropriate measures taken. Very rarely, precipitation of the calcium salt of ceftriaxone in renal has been observed in children over age 3, which could cause symptomatic or asymptomatic renal insufficiency. These effects resolved following discontinuance of the drug. In above case, high dosage (over 10 g/day) was administered to a patient who had a risk factor such as medicated over daily dosage, restricted water intake and mainly lain sick in bed.

6) GI system: Rarely severe enterocolitis with hemafecia such as pseudomembranous enterocolitis may occur. If abdominal pain and frequent diarrhea occur, appropriate measure such as

immediate discontinuation of CEFAXONE, should be taken. Also occasionally nausea, vomiting, loose stools, diarrhea or rarely abdominal pain, anorexia, etc. may occur.
7) Respiratory system: Since interstitial pneumonia, PIE syndrome etc. accompanied with fever, cough, dyspnea, abnormal chest X-ray, eosinophilia, etc. may rarely occur with other cephems, in case that such symptoms occur, further administration should be discontinued and appropriate measures such as administration of corticosteroids, etc. should be taken.
8) Superinfection: Rarely, stomatitis and candidiasis may occur.
9) Vitamin deficiency: Rarely, symptoms of vitamin K deficiency (hypoprothrombinaemia, hemorrhage tendency, etc.) and vitamin B deficiency (glossitis, stomatitis, anorexia, neuritis, etc.) may occur.
10) Others: Occasionally, headache and rarely vertigo, edema, precipitation in gallbladder, ventricular extra-systole, elevation of creatinine and mycosis in genital organ, etc.

■ UNDESIRABLE EFFECTS

Postmarketing Experience

Nervous system disorders: encephalopathy

Reversible encephalopathy has been reported with the use of cephalosporins, including ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.

■ CONTRAINDICATIONS

1) Patients with history of shock to ceftriaxone sodium.
2) Patients with hypersensitivity to cephalosporins.
3) Patients with hypersensitivity or history of hypersensitivity to penicillins.
4) Patients with hypersensitivity to anilide local anesthetics such as lidocaine, etc. (in case of i.m. injection)

■ PRECAUTIONS

1. In order to prevent appearance of the resistant microorganisms, susceptibility should be determined and treatment should be continued only for the minimum period of time required.
2. In order to predict adverse reaction such as shock, etc. patient history should be checked in detail and skin reaction test should be performed.
3. Emergency facilities should be prepared in case of the development of shock. (if anaphylactic shock occurs intravenous epinephrine has to be followed by a glucocorticoid injection). After administration, patients should be kept quiet and under adequate supervision.
4. It is desirable to perform laboratory test (hepatic function, renal function, blood etc.) at regular intervals during treatment.
5. Shadows which have mistaken for gallstones have been detected on sonograms of the

gallbladder, usually following doses higher than the standard recommended dose. These shadows are however, precipitates of ceftriaxone calcium which disappear on completion or discontinuation of CEFAXONE therapy. Rarely, these findings have been associated with symptoms. In symptomatic cases, conservative non-surgical management is recommended. Discontinuation of CEFAXONE treatment in symptomatic cases should be at the discretion of the clinician.

6. a) Pseudomembranous colitis has 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 the diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agent.
   b) Prolonged use of CEFAXONE may result in over- growth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.
7. CEFAXONE is not reported to have adverse effect on a person's ability to drive vehicles or operate machinery.
8. Careful administration
   1) Patients with history of drug allergy
   2) Patients oneself of whose parents, sisters or brothers are prone to suffer from allergic symptoms such as bronchial asthma, exanthema, urticaria, etc.
   3) Patients with severe renal disorder (as the plasma concentration is maintained for a long period of time, decreased dosage or increased interval between treatments are required)
   4) Patients with poor oral or parenteral nutrition patients, elderly patients, patients with poor general conditions (Cautious monitoring is required since vitamin K deficiency may occur).
9. Interference with laboratory test.
   1) Caution should be taken as urine-glucose test using Benedict's reagent Fehling's reagent, Clinitest, except for Testape reaction, may give false positive results.
   2) Caution should be taken as direct Cooms-test may give false positive results.
   3) CEFAXONE like other antibiotics may result in false-positive tests for galactosemia.
10. Precautions on application
   1) As vascular pain, venous thrombosis, flushing, nausea, vomiting may rarely occur by large intravenous dose, caution should be taken on preparation of injectable solution, site of injection, method of administration, etc., and infection should be given as slowly as possible. i.v injection)
   2) CEFAXONE should be used immediately after reconstitution. Particularly, caution should be taken when dissolving in glutathione preparation or high concentration amino acid solution.

■ DRUG INTERACTION

1. No impairment of renal function has so far been observed after concurrent administration of large doses of CEFAXONE and potent diuretic (e.g frusemide)

2. Synergy between CEFAXONE and aminoglycosides has been demonstrated with many Gram-negative bacilli under experimental conditions and it is of special importance in severe life-threatening infections due to microorganisms such as Pseudomonas aeruginosa. Be- cause of physical incompatibility the two drugs must be administered separately at the recommended dosages. There is no evidence that CEFAXONE increases renal toxicity of aminoglycosides.
3. No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of CEFAXONE.
4. The elimination of CEFAXONE is not altered by probenecid.
5. CEFAXONE does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.
6. In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

■ DOSAGE AND ADMINISTRATION
1. Adults and children over twelve years: 1~2g (potency) of ceftriaxone sodium is administered once daily intravenously or intramuscularly. In severe case or infections caused by moderately sensitive organisms, the dosage may be increased up to 4g (potency) once daily.
2. Neonates (14 days or below): A daily dose is 20~50 mg (potency)/kg bodyweight is administered once a day and not to exceed 50mg (potency)/kg. It is not necessary to differentiate between premature and infants born at term.
3. Infants and children (15 days to twelve years): daily dose of 20~80mg (potency)/kg is administered once a day. For children of 50 kg bodyweight or more, the usual adult dosage should be used. Intravenous doses of 50mg (potency)/kg or more should be given by infusion over at least 30minutes.
4. Elderly patients: In elderly patients, the dosages recommended for adults can be used without modification.
5. Meningitis: In bacterial meningitis in infants and children, treatment begins with doses of 100 mg (potency)/kg (not to exceed 4 g (potency)) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly.
The following duration of therapy has shown to be effective

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

6. Gonorrhea: For the treatment of gonorrhea (penicillinase-producing and nonpenicillinase-producing strains), a single i.m. dose of 250 mg (potency) is recommended.
7. Perioperative prophylaxis: To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended approach is single dose of 1~2g (potency) administered 30~90 minutes prior to surgery depending on the risk of infection. In colorectal surgery, concurrent (but separately administered) administration of CEFAXONE with or without 5-nitroimidazole (e.g. ornidazole) has proven effective.

8. Impaired renal and hepatic function: In patients with impaired renal function, there is no need to reduce the dosage of CEFAXONE if hepatic function is intact, but in case of preterminal renal failure (creatinine clearance <10ml/min>) the dosage should not exceed 2g (potency) daily. In patients with liver damage, there is no need for the dosage to be reduced if renal function is intact. In cases of combined severe renal and hepatic dysfunction, the plasma concentration of the ceftriaxone should be measured at regular intervals. In patients undergoing dialysis, no additional supplementary dosing is required after the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustment is necessary, since the elimination rate in these patients may be reduced.

○ Duration of therapy

The duration of therapy varies according to the recovery from the disease. In general, as with other antibiotic therapy, administration of the Cefaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

○ Preparation of injectable solution

1. Intramuscular injection: For i.m. injection, CEFAXONE 0.5g is dissolved in 2ml and CEFAXONE 1 g in 3.5 ml of 1% lidocaine hydrochloride solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1g is injected at one site. I.m injection without lidocaine solution is painful. The lidocaine solution must never be administered intravenously.

2. Intravenous injection: For I.V. injection, CEFAXONE 0.5 g is dissolved in 5ml, and CEFAXONE 1g in 10 ml sterile water for injection. The intravenous administration should be given over two to four minutes. In case of intravenous infusion, the infusion should last at least 30 minutes. For i.v. infusion, 2 g of CEFAXONE 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%, dextran 6% in dextrose 5%, hydroxyl ethyl starch 6~10% infusions or sterile water for injection. CEFAXONE 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.

Reconstituted solutions retain their physical and chemical stability for six hours when stored below 25°C or 24 hours at 2-8°C. As a general rule however, the solutions should be used immediately after reconstitution. Reconstituted solution has color ranging from pale yellow to amber, depending on the concentration and the length of storage. This characteristic of the active ingredient is of no significance for the efficacy or tolerance of the drug.

■ SYMPTOMS & TREATMENT OF OVERDOSAGE

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.

■ USE IN PREGANANCY, LACTATION & NEONATES

Pregnancy

1) CEFAXONE permeates placenta.
2) As safety in human pregnancy has not been established, CEFAXONE should not be administered to pregnant women or women of child bearing potential unless therapeutic benefit is considered to exceed the possible risk.
Lactation
As CEFAXONE is excreted in the breastmilk at low concentration, caution is advised in nursing mothers. Neonates and Prematures.
1) Safety on neonates and prematures has not been established.
2) Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Caution should be exercised when considering CEFAXONE treatment in hyperbilirubinemic neonates. CEFAXONE should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy.

■ INCOMPATIBILITIES: Calcium containing solution or with aminoglycosides, fluconazole, vancomycin or amsacrine.
■ STORAGE: Store in a hermetic container below 30℃
■ HOW SUPPLIED: 0.5 g/Vial × 10, 1 g/Vial × 10
■ SHELF LIFE: 3years from the manufacture date

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