CEFIXON

Vial

Composition
Each vial contains 1 g Ceftriaxone (as sodium).

Action
The bactericidal activity of Ceftriaxone results from inhibition of cell wall Synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinase and cephalosporinases, of gram-negative and gram-positive bacteria. Ceftriaxone is usually active against the following microorganisms in vitro and in clinical infections.

Gram-Negative Aerobes
Enterobacter aerogenes, En-terobacterclocae, *Escherichia coli Haemophilus influenza* (including ampicillin-resistant strains),H. para influenza ,Klebsiella species (including penicillinase and non penicillinase producing strains),*Neisseria meningitides*, *Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*. *Citrobacter freundii, Citrobacter diversus*, Provide species (including Providencia rettgeri), Salmonella species (including S. typhi), Shigella species and *Acinetobacter calcaceticus*.

Note: Many strains of the above organisms that are multiple resistant to other antibiotics, e.g. penicillins, cephalosporins and aminoglycosides, are susceptible to Ceftriaxone sodium.
Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*.

Gram-Positive Aerobes
Staphylococcus aureus (including penicillinase -producing strains) and *Staphylococcus epidermidis*.

Note: methicillin-resistant staphylocci are resistant to cephalosporins, including Ceftriaxone), Streptococcus Pyogenes (Group A beta-hemolytic streptococci), Streptococci agalactiae (Group B streptococci) and *Streptococcus pneumoniae*. (Note:Most strains of enterocci, *Streptococcus pneumoniae*. (Note:Most strains of enterocci, *Streptococcus faecalis* and Group D streptocci are resistant).
Ceftriaxone also demonstrates in vitro activity against the following microorganisms, although the clinical significance is unknown:

Anaerobes
Bacteroides species, Clostridium species (Note: most strains of C.difficile are resistant).

Pharmacokinetics
The maximum plasma concentration after a single IM dose of 1.0 g is about 81 mg/l and is reached in 2-3 hours after the dose. 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.

On intravenous administration, ceftriaxone diffuses into the tissue fluid, where-if it is given in the recommended dosage range-bactericidal concentrations lasting 24 hours may be maintained. 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/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.

The volume of distribution of ceftriaxone is 7-12 L. After a dose of 1-2 g, concentrations above the minimal inhibitory concentrations of most pathogens responsible for infection are detected for more than 24 hours in the following tissues or body fluids: lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone; and cerebral, pleural, prostatic, and synovial fluids.

In healthy, young adults, the total plasma clearance is 10-22 ml/min. The 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 eight hours. The substance is largely inactivated in the faeces due to metabolism by intestinal flora.

The mean plasma elimination half-life is 8 hours in healthy, young adults. 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 2-3 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.

In meningitis patients, administration of 50 mg per kg body mass leads within 2-24 hours to cerebro spinal fluid concentrations several times as high as the minimum *in vitro* inhibitory concentrations required for the most common causative organisms of meningitis.

Indications

Cefixon is indicated for the treatment of the following infections when caused by susceptible organisms.

Lower respiratory tract infections
Caused by Strep. Pneumoniae, Streptococcus species (excluding enterococci), Staph. Aureus,H. influenza, H. para influenza, Klebsiella species (including K. pneumoniae), E.coli, E. aerogenes, *Proteus mirabilis* and *Serratia marcescens*.

Skin and Skin Structure Infections
Caused by staph.aureus, Staph. Epidermidis, Streptococcus species (excluding enterococci), E.cloacae, Klebsiella species (including K.pneumoniae), *Proteus mirabilis* and *Pseudomonas aeruginosa.*

Urinary Tract Infections
(Complicated and uncomplicated) caused by E.coli, *Proteus mirabilis*, *Proteus vulgaris*, M. morganii and Klebsiella species (including K. pneumoniae).

Uncomplicated Gonorrhea
(Cervical / urethral and rectal) caused by *Neisseria gonorrhea*, including both penicillinase and non penicillinase producing strains, and pharyngeal gonorrhea caused by non penicillinase producing strains of Neisseria gonorrhea.

Pelvic
Caused by N. gonorrhea.

Bacterial Septicemia
Caused by Staph. Aureus, Strep. Pneumonia, E.coli, H. influenza and K. pneumoniae.

Bone and Joint Infections
Caused by Staph. Aureus, Strep. Pneumoniae, Streptococcus species (excluding enterococci). E.coli,P.mirabilis,K.pnemoniae and Enterobacter species.

Intra-Abdominal Infections
Caused by E. coli and K.pneumoniae.

Meningitis

Caused by H. influenzae, N.meningitidis and Strep. Pneumoniae. Cefixon has also been used successfully in a limited number of cases of meningitis and shunt infections caused by Staph. Epidermidis and E. coli.

Surgical Prophylaxis
The preoperative administration of a single 1 gm dose of Cefixon may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal or abdominal hysterectomy) and in surgical patients for whom infection at the operative site would present serious risk (e.g., during coronary artery bypass surgery).

Although Ceftriaxone has been shown to have been as effective as Cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

When administered prior to surgical procedures, for which it is indicated, a single 1 GM dose of Ceftriaxone provides protection from most infections due to susceptible organisms throughout the course of the procedure.

Susceptibility Testing
Before instituting treatment with Ceftriaxone, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

Contraindications
Ceftriaxone is contraindicated in-patients with known allergy to the cephalosporin class of antibiotics.

Warnings
Before therapy with Ceftriaxone is instituted careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins penicillin's or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

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 this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of " antibiotic associated colitis."After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against C. Difficile.

Precautions
General
Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Ceftriaxone is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone are administered, but

concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Ceftriaxone dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients with impaired vitamin K synthesis or low vitamin K stored (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Ceftriaxone may result in overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If super infection occurs during therapy, appropriate measures should be taken.

Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis. Rare cases have been reported in which sonographic abnormalities are seen in the gallbladder of patients treated with Ceftriaxone; these patients may also have symptoms of gallbladder disease. These abnormalities are variously described as slug, precipitation, echoes with shadow, and may be misinterpreted as concretions. The chemical nature of the sonographically detected material has not been determined.

The condition appears to be transient and reversible when Ceftriaxone is discontinued and conservative management employed . Therefore, Ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and / or the sonographic findings described above.

Pregnancy
Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers
Low concentrations of Ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described in the Dosage and Administration section In vitro studies have shown that Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to hyperbilirubinemic neonates, especially premature.

Adverse Reactions
Ceftriaxone is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Ceftriaxone therapy or of uncertain etiology, were observed.

Local reactions-pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I.V. administration.

Hypersensitivity
Rash (1.7%), less frequently reported (less than 1%) were pruritus, fever or chills.

Hematologic

Eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia, and prolongation of the prothrombin time.

Gastrointestinal
Diarrhea (2.7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hepatic
Elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

Renal
Elevations of the BUN (1.2 %) were elevations of creatinine and the presence of casts in the urine.

Central Nervous System
Headache or dizziness was reported occasionally (less than 1%).

Genitourinary
Moniliasis or vanities were reported occasionally (less than 1%).

Miscellaneous
Diaphoresis and flushing were reported occasionally (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

Dosage and Administration

Standard dosage
Adults and children over 12 years. The usual dosage is 1-2 g of Cefixon *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.
Neonates, infants, and children up to 12 years. The following dosage schedules are recommended for *once daily* administration:

Neonates (up to 14 days): 20-50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. It is not necessary to differentiate between premature and term infants.

Infants and children (15 days to 12 years): 20-80 mg/kg once daily.

For children with body weights of 50 kg or more, the usual adult dosage should be used.

Intravenous doses of ≥50 mg/kg bodyweight should be given by infusion over at least 30 minutes.
Elderly patients. The dosages recommended for adults require no modification in 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 Cefixon 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 Cefixon 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*, treatment begins with doses of 100 mg/kg (up to a maximum of 4 g) 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

Gonorrhoea (penicillinase-producing and nonpenicillinase-producing strains): a single i.m. dose of 250 mg.
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 Cefixon with or without a 5-nitroimidazole, has been proven effective.

Impaired renal and hepatic function: In patients with *impaired renal function*, there is no need to reduce the dosage of Cefixon *provided hepatic function is intact*. Only in cases of preterminal renal failure (creatinine clearance <10 ml/min) should the Cefixon 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*, is monitored to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

Directions for Use
Intramuscular Administration
After reconstitution, each 1 ml of solution contains approximately 250 mg equivalent of Ceftriaxone. If required, more dilute solutions could be utilized. As with all intramuscular preparations, Ceftriaxone should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Intravenous Administration
Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes. Concentrations between 10 mg/ml and 40 mg/ml are recommended; however, lower concentrations may be used if desired. Reconstitute vials or "piggyback" bottles with and appropriate I.V. diluents.

After reconstitution, each 1 ml of solution contains approximately 100 mg equivalent of Ceftriaxone.

Withdraw entire contents and dilute to the desired concentration with the appropriate I.V. diluents.

Dosage Size	**Amount of diluents *to be added***
1 gm	10 ml
2 gm	20 ml

After reconstitution, further dilute to 50 ml or 100 ml volumes with the appropriate I.V. diluents.

Presentation
Cefixon vial
Box of one vial, Box of 5 vials

Cefixon with lidocaine
Box of 1 vial and 1 amp of lidocaine 1% for IM administration