NEW ZEALAND DATA SHEET

1. CEFTRIAXONE-AFT powder for injection

Ceftriaxone-AFT 500 mg powder for injection.
Ceftriaxone-AFT 1 g powder for injection.
Ceftriaxone-AFT 2 g powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ceftriaxone-AFT 500 mg: each vial contains 500 mg ceftriaxone (as sodium).
Ceftriaxone-AFT 1 g: each vial contains 1 g ceftriaxone (as sodium).
Ceftriaxone-AFT 2 g: each vial contains 2 g ceftriaxone (as sodium).

Excipients with known effect:
Each gram of ceftriaxone contains approximately 83 mg (3.6 mmol) of sodium.

3. PHARMACEUTICAL FORM

Powder for injection.
White to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone-AFT is indicated in the treatment of the following infections when caused by susceptible aerobic organisms:

Lower Respiratory Tract Infections
Caused by *S. pneumoniae,* Streptococcus spp (excluding enterococci), methicillin sensitive *S, aureus, H. influenzae, H. parainfluenzae, Klebsiella sp* (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcesens.*

Skin and Skin Structure Infections
Caused by methicillin sensitive *S. aureus* and *S. epidermidis,* Streptococcus Group B, Streptococcus Group G, *Streptococcus pyogenes, Streptococcus viridans,* Streptococcus spp (excluding enterococci), Peptostreptococcus spp, *E. coli, E. cloacae,* Klebsiella spp (including *K. pneumoniae, K. oxytoca*), *Proteus mirabilis, Morganella morganii, Serratia marcescens.*

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

Uncomplicated Gonorrhoea
Cervical, urethral and rectal caused by *Neisseria gonorrhoea* (both penicillinase and non-penicillinase producing strains).

Bacterial Septicaemia

Caused by *S. pneumoniae, E. coli,* and *H. influenzae*.

Bone Infections
Caused by methicillin sensitive *S. aureus, methicillin sensitive S. epidermidis,* Streptococcus group B, *S. pneumoniae,* Streptococcus spp (excluding enterococci), *E. coli,* Enterobacter spp, *P mirabilis* and *K. pneumoniae.*

Joint Infections
Caused by methicillin sensitive *S. aureus, S. pneumoniae,* Streptococcus spp (excluding enterococci), *E. coli, P mirabilis K. pneumoniae* and Enterobacter spp.

Meningitis
The initial treatment as a single agent of meningitis in children and immunocompetent adults when presumed or proven to be caused by *Haemophilus. influenzae* type b, *Neisseria meningitides, Streptococcus pneumoniae* or Enterbacteriaceae pending culture and sensitivity results.

Surgical Prophylaxis
The pre-operative administration of a single 1 g dose of ceftriaxone may reduce the incidence of post-operative infections in patients undergoing vaginal or abdominal hysterectomy or cholecystectomy in high-risk patients, surgical procedures which are classified as contaminated or potentially contaminated and patients undergoing 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.

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 before obtaining the results of susceptibility testing.

4.2 Dose and method of administration

Dosage
Ceftriaxone-AFT may be given either I.M. or I.V. The recommended adult daily dose is 1-2 g given once daily or in equally divided doses twice daily depending upon the type and severity of the infection. The lower dose is appropriate for less severe infections.

Uncomplicated gonococcal infections
A single I.M. dose of 500 mg.

Surgical prophylaxis
In cardiovascular surgery, biliary tract surgery in high risk patients and vaginal and abdominal hysterectomy a single dose of 1 g given 0.5-2 hours prior to surgery.

Children
For treating serious miscellaneous infections in children the recommended total daily dose is 50-75 mg/kg (not more than 2 g), given once daily or in divided doses every 12 hours. In meningitis the dose should be divided and given 12 hourly.

Generally ceftriaxone therapy should be continued for at least 2 days after the signs and symptoms of the infection have disappeared. The usual duration of treatment is 4-14 days. In special conditions e.g. endocarditis, osteomyelitis, infected joints etc. treatment may be continued for a longer duration. Prolonged therapy results in a higher incidence of adverse effects especially diarrhoea, rash, eosinophilia, elevated liver enzymes and to a lesser extent neutropenia.

When treating infections caused by Strepococcus pyogenes therapy should be continued for at least 10 days.

Use in renal and hepatic impairment
No dosage adjustment is necessary for patients with impairment of hepatic function however blood levels should be monitored in patients with severe renal impairment e.g. dialysis patients and in patients with both renal and hepatic dysfunction. Serum levels should not exceed 280 µg/mL.

Administration
Ceftriaxone-AFT contains no microbial preservative. It is for single use in one patient only. Any unused product should be discarded. To reduce any microbial hazard, use as soon as practicable after reconstitution.

The use of freshly prepared solutions is recommended. Solutions retain their efficacy for 6 hours at room temperature or 24 hours when stored in the refrigerator (2-8 ºC). The solutions are yellowish in colour. This characteristic of the active ingredient is of no significance to the efficacy or tolerance of the medicine. A slight opalescence may be seen in the reconstituted solution.

Do not use diluents containing calcium such as Ringer's solution or Hartmann's solution to reconstitute Ceftriaxone-AFT vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone calcium can also occur when Ceftriaxone-AFT is mixed with calcium containing solutions in the same I.V. administration line. Ceftriaxone-AFT must not be administered simultaneously with calcium containing solutions such as parenteral nutrition via a Y-site. However, in patients other than neonates Ceftriaxone-AFT and calcium containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (See Contraindications).

There have been no reports of an interaction between ceftriaxone and oral calcium containing products or interaction between intramuscular ceftriaxone and calcium containing products given either I.V. or orally.

Ceftriaxone-AFT should not be mixed with or piggybacked into solutions containing other anti- microbial medicines or into diluent solutions other than those listed below owing to possible incompatibility. Specifically, the literature reports that ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Intramuscular Administration
Dissolve 500 mg of Ceftriaxone-AFT in 2 mL or 1 g of Ceftriaxone-AFT in 3.5 mL lignocaine solution (1%). It should be administered by deep intragluteal injection. It is recommended that no more than 1 g be injected on either side. The lignocaine solution must never be given intravenously. Ceftriaxone-AFT should be injected well into the body of a relatively large muscle mass. I.M. injection of Ceftriaxone- AFT is painful without lignocaine.

Intravenous Administration
Ceftriaxone-AFT may be administered by intravenous injection or by continuous or intermittent infusion.

Intravenous Injection:
Dissolve 500 mg in 5 mL or 1 g in 10 mL sterile water for injection and administer by direct I.V. injection given over a period of 2-4 minutes.

Intravenous Infusion:
Dissolve 2 g Ceftriaxone-AFT in approximately 40 mL of one of the following infusion solutions:

- Sodium chloride 0.9%
- Sodium chloride 0.45% + glucose 2.5%
- Glucose 5%
- Glucose 10%
- Levulose 5%
- Dextran 70 6% in glucose 5%

The infusion should be given over a period of at least 30 minutes.

4.3 Contraindications

Ceftriaxone is contraindicated in patients with known allergies to the cephalosporin group of antibiotics or a major allergy to penicillin (anaphylaxis, angioneurotic oedema, urticaria).

Lignocaine should not be used as a diluent for I.M. administration in patients who are hypersensitive to lignocaine.

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.

Because of the risk of precipitation of ceftriaxone calcium, ceftriaxone is contraindicated in neonates requiring (or expected to require) treatment with calcium containing I.V. solutions including continuous calcium containing infusions such as parenteral nutrition (See Special warnings and precautions for use).

Interactions with other medicines and a small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium containing fluids. In some of these cases, the same I.V. line was used for both ceftriaxone and the calcium containing solution and in some a precipitate was noted in the I.V. infusion line. At least one fatality has been reported in a neonate who received ceftriaxone and calcium containing fluids at different time points via different I.V. lines – no crystalline material was observed at autopsy in this neonate. There have been no similar reports for patients other than neonates.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before therapy with Ceftriaxone-AFT therapy is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins 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. Anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed to ceftriaxone or other cephalosporins. Serious acute hypersensitivity reactions may require the use of subcutaneous adrenaline and other emergency measures. If an allergic reaction occurs ceftriaxone should be discontinued.

Calcium containing solutions

In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing products. However ceftriaxone should not be mixed with or administered to any patient simultaneously with calcium-containing solutions even via different infusion lines. (See Contraindications, Interactions with other medicines and other forms of interactions).

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including ceftriaxone and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Toxin hyperproducing strains of *C. difficile* cause increased morbidity and mortality as these infections can be refractory to antibiotic

therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary as CDAD has been reported to occur over 2 months after administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile* and surgical intervention should be instituted as clinically indicated.

Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong or worsen the condition and should not be used.

Other causes of colitis should also be considered.

History of Gastro-Intestinal Disease

Ceftriaxone should be prescribed with caution in patients with a history of gastrointestinal disease especially colitis.

Immune mediated Haemolytic Anaemia

Immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while on ceftriaxone the diagnosis of cephalosporin associated anaemia should be considered and ceftriaxone discontinued until the etiology is determined.

Overgrowth of Non-susceptible Organisms

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

Pancreatitis and Biliary Precipitation

Cases of pancreatitis (possibly of biliary obstruction aetiology) have been reported in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge. e.g., preceding major therapy, severe illness and total parenteral nutrition. A trigger or co-factor role of ceftriaxone related biliary precipitation can therefore not be ruled out.

Gallbladder Concretions/Precipitates

Shadows which have been mistaken for gall stones have been detected on sonograms of the gallbladder usually following doses higher than the recommended standard dose. These shadows are however precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy. Rarely have these finding been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended. Discontinuation of ceftriaxone therapy in symptomatic cases should be at the discretion of the physician.

Alterations in Clotting Time

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

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal

necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, Ceftriaxone-AFT should be discontinued immediately and an alternative treatment should be considered.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Special patient populations

Use in hepatic impairment

Repeated use of lignocaine hydrochloride should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).

Use in renal impairment

Ceftriaxone has shown some evidence of renal toxicity in animals. Clinical studies have shown only transient elevations of serum urea and serum creatinine at the recommended dosages.

Ceftriaxone is excreted by both biliary and renal excretion (See Pharmacokinetic properties). The half-life of ceftriaxone may be prolonged in some patients with renal failure, adjustment in dosage may be required. Concentrations of drug in the serum should be periodically monitored. If evidence of accumulation exists the dosage should be reduced accordingly. Dosage adjustments should not be necessary in patients with hepatic dysfunction. In patients with both hepatic dysfunction and significant renal disease ceftriaxone dosage requires close monitoring of serum concentrations.

Use in the elderly

No data available

Paediatric use

The safety and efficacy of ceftriaxone in infants and children have been established for the doses 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 given to neonates who may be at risk of developing bilirubin encephalopathy (especially premature infants) (See Contraindications). Because of the risk of precipitation of ceftriaxone-calcium (See Interactions with other medicines and other forms of interactions), ceftriaxone is contraindicated in neonates requiring or expected to require treatment with calcium containing I.V. solutions including continuous calcium containing infusions such as parenteral nutrition (See Contraindications).

Effects on laboratory tests

In patients treated with ceftriaxone, the Coombs' test may become false positive. Ceftriaxone like other antibiotics may result in false positive tests for galactosemia.

Likewise non-enzymatic methods for glucose determination in urine may give false positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

Haematological changes such as eosinophilia, leucopenia, granulocytopenia, haemolytic anemia, thrombocytopenia, isolated cases of agranulocytosis (<500/mm^3) have been reported mostly after 10 days of treatment and following doses of 20 g or more. During prolonged treatment the complete blood counts should be done at regular intervals.

4.5 Interaction with other medicines and other forms of interaction

Ceftriaxone does not contain an N-methylthiotetrazole moiety which has been associated with significant impairment of Vitamin-K dependent coagulation by some other cephalosporins.

Probenecid does not cause any clinically significant changes in the elimination of ceftriaxone. Concomitant use does not confer any therapeutic benefit.

In an *in vitro* study antagonists effects have been observed with the combination of chloramphenicol and ceftriaxone.

Do not use calcium containing diluents e.g. Ringer's or Hartmann's solutions to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone calcium can also occur when ceftriaxone is mixed with calcium containing solutions in the same I.V. administration line. Ceftriaxone must not be administered simultaneously with calcium containing I.V. 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 are at an increased risk of precipitation of ceftriaxone calcium (See Contraindications and Dose and method of administration).

No impairment of renal function has so far been observed after concurrent administration of ceftriaxone and diuretics e.g. frusemide. Healthy adults treated with 3 mg ceftriaxone and 3 mg/kg/day of tobramycin for 3 days did not show any enzymatic evidence of impaired renal function.

Based upon literature reports ceftriaxone is physically incompatible in admixtures with amsacrine, vancomycin, fluconazole and aminoglycosides.

4.6 Fertility, pregnancy, and lactation

Pregnancy Category B1

Teratogenic Effects

Reproduction studies (Segment II) have been performed in rats and mice at doses up to 586 mg/kg/day and no evidence of embryotoxicity, foetotoxicity or teratogenicity was seen. In primates at doses up to 84 mg/kg/day no embryotoxicity, foetotoxicity or teratogenicity was demonstrated.

There are however, no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

Non-tetatogenic Effects
In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and post-natal studies) with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation including post-natal growth, functional behaviour and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

Breast-feeding
Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a nursing woman.

Fertility
Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Ceftriaxone is generally well tolerated. In clinical trials the following adverse effects, which were considered to be related to ceftriaxone therapy or of uncertain aetiology were observed. Their incidence was somewhat higher in children and with higher doses.

Local Reactions
Infrequent pain, induration or tenderness at the site of injection. Less frequently reported was phlebitis after I.V. administration. Local reactions were increased if water was used as diluent instead of lignocaine.

Hypersensitivity
Infrequent rash. Less frequently, pruritus, fever or chills, severe dermatitis including exfoliative erythroderma, anaphylaxis, erythema multiforme, urticaria, exanthema and allergic dermatitis.

Haematological
Occasionally eosinophilia, thrombocytosis, leucopenia. Less frequently haemolytic anaemia, neutropenia, lymphopenia, granulocytopenia, thrombocytopenia and prolongation of the prothrombin time and bleeding. Very rare cases of agranulocytosis have been reported.

Gastrointestinal
Occasional diarrhoea. Less frequently nausea, vomiting, stomatitis, glossitis and dysgeusia. The incidence of diarrhoea tends to be higher in women and children. Pseudomembranous colitis has been reported rarely.

Hepatic
Occasional elevations of SGOT or SGPT. Less frequently elevations of alkaline phosphatase and bilirubin. Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder. Hepatitis and hepatic cholestatic (frequency unknown)

Renal
Infrequent elevations of serum urea. Less frequently elevations of creatinine and the presence of casts in the urine. Rare cases of crystalluria and oliguria have been reported. Renal adverse effects are reported more frequently in the elderly.

Central Nervous System
Occasionally headache and dizziness
Encephalopathy (rare)

Genitourinary
Occasionally moniliasis, and vaginitis.

Miscellaneous
Occasionally diaphoresis, flushing and fever. Rarely observed adverse reactions include leukocytosis, lymphocytosis, monocytosis, basophilia, jaundice, glycosuria, haematuria, broncospasm, oedema, shivering, serum sickness, abdominal pain, flatulence, dyspepsia, palpitations and epistaxis have been reported.

Isolated cases of Stevens Johnson syndrome and Lyell's Syndrome (toxic epidermalnecrolysis) have been reported.

Post Marketing Experience
Nervous system disorders: Seizures, myoclonus – frequency not known.

Cases of fatal reactions with calcium ceftriaxone precipitates in lungs and kidneys in neonates and premature infants have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium containing solutions differed. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions or products even via different infusion lines (See Contraindications).

Interaction with Calcium
Two *in vitro* studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess the interaction between ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 g of ceftriaxone infused over 30 minutes) were used on combination with calcium concentrations of up to 12 mM (48 mg/100 mL) in adult plasma. Recovery of ceftriaxone from plasma was reduved with calcium concentrations of 6 mM (24 mg/100 mL) or higher in adult plasma or 4 mM (16 mg/100 mL) or higher in neonatal plasma. This may be reflective of ceftriaxone calcium precipitation (See Contraindications).

Skin and Other Subcutaneous Tissue Disorders
Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in beta-lactam antibiotics.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/}

4.9 Overdose

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, third-generation cephalosporins, ATC code: J01DD04.

Mechanism of action

Microbiology

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, types I, II & III, both penicillinases and cephalosporinases, of gram-negative and grampositive bacteria. It is susceptible to type IV beta lactamases at approximately 18% of the rate of cephaloridine. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (See Therapeutic indications).

GRAM-NEGATIVE AEROBES: *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), Klebsiella species (including *K. pneumoniae). Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens.*

Note: Strains of the above organisms that are multiple resistant to other antibiotics, e.g. penicillins, cephalosporins and aminoglycosides, may be susceptible to ceftriaxone sodium. Ceftriaxone is also active against some strains of *Pseudomonas aeruginosa.* Other pseudomonas species are usually resistant.

GRAM-POSITIVE AEROBES: *Staphylococcus aureus* (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note: methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta-haemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* Group G streptococci, *Streptococcus viridans* and Streptococcus species (Note: Most species of Group D streptococci including *Streptococcus faecalis* and *Streptococcus faecium* are resistant).

SUSCEPTIBILITY TESTING: Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, Am J Clin Pathol 45:493-496, 1966; Standardized Disk Susceptibility Test, Federal Register 39: 19182-19184, 1974: National Committee for Clinical Laboratory Standards Approved Standard: ASM-2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone. Laboratory results of the standardized single-disk susceptibility test using a 30 µg ceftriaxone disk should be interpreted according to the following three criteria:

1. Susceptible organisms produce zones of 21 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that produce zones of 14 to 20 mm are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g. urine), in which high antibiotic levels are attained.
3. Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks.

Standardized procedures require use of control organisms. The 30 µg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853, respectively.

DILUTION TECHNIQUES: A bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 8 µg/mL. Organisms are considered resistant to ceftriaxone if the MIC is greater than 32 µg/mL. Organisms having a MIC value of equal to or less than 32 µg/mL, but greater than 8 µg/mL, are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg urine), in which high antibiotic levels are attained. *E. coli* ATCC 25922, S. aureus ATCC 25923 and P. aeruginosa ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests. Greater than 95% of MICs for the E. *coli* strain should fall within the range of 0.016 to 0.5 µg/mL. The range for the *S.aureus* strain should be 1 to 2 µg/mL.

5.2 Pharmacokinetic properties

Absorption

Ceftriaxone is poorly absorbed from the gastrointestinal tract.

Distribution

Average plasma concentrations in µg/mL following a single 30 minute I.V. infusion of a 0.5, 1 or 2 g dose and I.M. administration of a single 0.5 or 1 g dose are presented in Table 1.

Table 1: Average Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/ route	Average plasma concentrations (µg/mL) (Time from end of administration in hours)								
	0.5	1	2	4	6	8	12	16	24
500 mg I.V.	82	59	48	37	29	23	15	10	5
500 mg I.M.	30	41	43	39	31	25	16	ND	ND
1 g I.V.	151	111	88	67	53	43	28	18	9
1 g I.M.	40	68	76	68	56	44	29	ND	ND
2 g I.V.	257	192	154	117	89	74	46	31	15

I.V. doses infused at constant rate over 30 minutes IM doses administered with lignocaine
ND = not determined

Mean maximum plasma concentrations following I.M. injection occurred 2-3 hours post-dosing. Multiple I.M .and I.V doses ranging between 500 mg-2 g at 12-24 hourly intervals resulted in 15-36% accumulation of ceftriaxone above single dose results. Accumulation was greater with I.M. doses.

Ceftriaxone concentrations in urine are high as shown in Table 2.

Table 2: Urinary Concentrations (µg/mL) of Ceftriaxone after Single Dose Administration

Dose/route	Average urinary concentrations (µg/mL)				
	0 -2 hours	2 -24 hours	4 – 8 hours	8 –12 hours	12-24 hours
500 mg I.V.	526	366	142	87	70
500 mg I.M.	115	425	308	127	96
1 g I.V.	995	855	293	147	132
1 g I.M.	504	628	418	237	ND
2 g I.V.	2692	1976	757	274	198

ND = Not determined

Over a 0.15 to 3 g dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours, apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hr and renal clearance from 0.32 to 0.73 L/hr. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of 25 µg/mL to a value of 85% bound at 300 µg/mL. Protein binding is reduced in children and in uremic patients. The *in vitro* activity of ceftriaxone is decreased 2 to 8 fold by the presence of human serum.

Excretion

33 – 67% of a ceftriaxone dose is excreted in the urine as the unchanged drug. Substantial amounts are secreted in the bile and eventually found in the faeces as microbiologically inactive compounds. A small fraction appears in the urine as an unidentified metabolite. Renal excretion of ceftriaxone is not affected by prior administration of probenecid. After a 1 g I.V. dose, average ceftriaxone concentrations, determined from 1-3 hours after dosing were 581 µg/mL in the gallbladder bile , 788 µg/mL in the common duct bile, 898 µg/mL in the cystic duct bile, 78.2 µg/mL in the gallbladder wall and 62.1 µg/mL in the concurrent plasma. There were however, wide individual variations in levels.

Pharmacokinetics in Paediatric Patients

The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after 50 mg/kg I.V. doses in paediatric patients suffering from bacterial meningitis are shown in Table 3.

Table 3: Average Pharmacokinetic Parameters of Ceftriaxone in Paediatric Patients

Pharmacokinetic parameter	**50 mg/kg I.V.**
Maximum plasma concentrations (µg/mL)	216
Elimination half-life (hour)	4.6
Plasma clearance (mL/hour/kg)	49
Volume of distribution (mL/kg)	338
Cerebral spinal fluid concentrations (in purulent meningitis) (µg/mL)	5.6
Range (µg/mL)	1.3-18.5
Time after dose (hour)	3.7 (±1.6)

The half-life of ceftriaxone in neonates ranges from 7.2 - 19 hours and in infants over six weeks of age from 4.0-6.6 hours.

Ceftriaxone crosses the placenta and appears in the milk in low concentrations.

Pharmacokinetics in the Elderly or those with renal or Hepatic Impairment

Compared to that in healthy adults, the pharmacokinetics of ceftriaxone are only minimally altered in the elderly or in patients with hepatic dysfunction (Table 4); therefore dosage adjustments are not necessary for these patients with doses of up to 2 g/day. However in some patients with severely impaired renal function the t½ of ceftriaxone may be prolonged (37-52 hours) and dosage adjustment should be considered. Peak serum levels should held below 280 µg/mL. Ceftriaxone is not removed from the plasma to any significant extent by haemodialysis. Plasma concentrations of ceftriaxone should be monitored to determine if dosage adjustments are necessary.

Table 4: Average Pharmacokinetic Parameters of Ceftriaxone in Humans

Patient Group	Elimination half-life (h)	Plasma clearance (L/h)	Volume of distribution (L)	Renal clearance (L/hr)
Healthy (dose range 0.15-0.3 g)	5.8 – 8.7	0.58 – 1.45	5.8 – 13.5	0.32 – 0.73
Elderly	8.9	0.83	10.7	
Renal Impairment Haemodialysis (< 5mL/min)* Severe (5 – 15 mL/min) Moderate (16 – 30 mL/min) Mild (31-60 mL/min)	 14.7 15.7 11.4 12.4	 0.65 0.56 0.72 0.70	 13.7 12.5 11.8 13.3	
Hepatic disease	8.8	1.1	13.6	

* Creatinine clearance

5.3 Preclinical safety data

Genotoxicity

Genetic toxicity tests including the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Carcinogenicity

Carcinogenicity studies with ceftriaxone in animals to determine the toxicity and carcinogenic potential of ceftriaxone have not been performed. The maximum duration of animal toxicity studies was 6 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

Ceftriaxone should not be added to solutions containing calcium such as Hartmann's solution and Ringer's solution. Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin and fluconazole and aminoglycosides.

Ceftriaxone-AFT should not be mixed with or piggybacked into solutions containing other anti- microbial medicines or into diluent solutions other than those listed below owing to possible incompatibility. Specifically the literature reports that ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides

6.3 Shelf life

Powder: 36 months.
Reconstituted solution: To reduce microbiological hazards, use as soon as practicable after reconstitution. The reconstituted solutions of Ceftriaxone-AFT are physically and chemically stable for 6 hours at room temperature and for 24 hours if stored under refrigeration (2-8 oC). Do not freeze reconstituted Ceftriaxone-AFT.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Ceftriaxone-AFT is supplied in glass vials closed with a rubber stopper and a flip-off cap, in pack sizes of 1, 5 or 10 vials.

6.6 Special precautions for disposal and other handling

Ceftriaxone powder must be reconstituted prior to use.

As a general rule, the solution should be used immediately after preparation. Reconstituted solutions retain their physical and chemical stability for six hours at room temperature or 24 hours under refrigeration (2-8 °C).

The solutions range in colour 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.

For IM injection, Ceftriaxone-AFT 1 g is dissolved in 3.5 mL of 1% lidocaine hydrochloride solution.

For IV injection, Ceftriaxone-AFT 500 mg is dissolved in 5 mL, or Ceftriaxone-AFT 1 g in 10 mL, of sterile water for injections.

For IV infusion, 2 g ceftriaxone are dissolved in 40 mL of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + glucose 2.5%, glucose 5%, glucose 10%, dextran 6% in glucose 5% and levulose 5%.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

13 January 2011

10. DATE OF REVISION OF THE TEXT

29 September 2025

Summary table of changes:

Section changed	Summary of new information
4.2	The dose for Uncomplicated gonococcal infections has been updated.