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## 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

Infections caused by pathogens sensitive to ceftriaxone 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.

#### 4.2 Dose and method of administration

##### Dose

*Adults and children over twelve years*

The usual dosage is 1-2 g of ceftriaxone administered once daily (every 24 hours). In severe cases or in

infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, administered once daily.

#### *Elderly patients*

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

#### *Paediatric population*

The following dosage schedules are recommended for once daily administration:

Neonates (up to 14 days): A daily dose of 20-50 mg/kg bodyweight, 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 infants born at term.

Infants and children (15 days to twelve years): A daily dose of 20-80 mg/kg.

NOTE: For children with bodyweights of 50 kg or more, the usual adult dosage should be used. Intravenous doses of 50 mg or more per kg should be given by infusion over at least 30 minutes.

#### Duration of therapy

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for a minimum of 48 to 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 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 (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. Effective results have been found with the following duration of therapy:

Neisseria meningitides	4 days
Haemophilus influenza	6 days
Streptococcus pneumoniae	7 days

##### *Gonorrhoea*

For the treatment of gonorrhoea (penicillinase-producing and nonpenicillinase-producing strains), a single IM dose of 250 mg ceftriaxone is recommended.

### *Perioperative prophylaxis*

To prevent postoperative infections in contaminated or potentially contaminated surgery, the recommended approach – depending on the risk of infection – is a single dose of 1 – 2 g ceftriaxone administered 30-90 minutes prior to surgery. In colorectal surgery, concurrent (but separate) administration of ceftriaxone with or without a 5-nitroimidazole, e.g. ornidazole, has proven effective.

### *Impaired renal and hepatic function*

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is intact. Only in cases of preterminal renal failure (creatinine clearance <10 mL/min) should the ceftriaxone 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 cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary the dose adjusted.

In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Plasma concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

### Method of administration

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.

Do NOT use diluents containing calcium, e.g. Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone. Particulate formation can result.

Ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites.

Calcium-containing solutions or products must not be administered with 48 hours of last administration of ceftriaxone.

For instructions on reconstitution of the medicine before administration, see section 6.6.

### *Intramuscular injection*

For IM injection, Ceftriaxone-AFT 500 mg is dissolved in 2 mL and Ceftriaxone-AFT 1 g is dissolved 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 1 g to be injected at one site.

The lidocaine solution must never be administered intravenously.

#### *Intravenous injection*

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. The intravenous administration should be given over two to four minutes.

#### *Intravenous infusion*

The infusion should last at least 30 minutes.

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% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl starch 6-10% infusions, sterile water for injections.

Ceftriaxone 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.

### **4.3 Contraindications**

Ceftriaxone is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Ceftriaxone is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to cephalosporin or penicillin.

Ceftriaxone is contraindicated in hyperbilirubinemic neonates, especially prematures. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Ceftriaxone must not be co-administered with calcium-containing IV solutions, including continuous calcium-containing infusions such as parental nutrition, in neonates because of the risk of precipitation of ceftriaxone-calcium salt. Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonate have been described. In some cases the infusion lines and the times of administration of ceftriaxone and calcium-containing solutions differed.

### **4.4 Special warnings and precautions for use**

Hypersensitivity reactions may occur in susceptible individuals.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Anaphylactic shock requires immediate countermeasures.

#### Hepatitis and hepatocellular injury

Cases of hepatitis and hepatocellular injury with or without jaundice have been observed during ceftriaxone therapy and may occur early in the treatment period and independently of cholelithiasis.

Patients should be advised to report immediately any symptoms suggestive of liver injury.

#### Antibiotic associated pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ceftriaxone. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

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

Other causes of colitis should be considered.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Superinfections with non-susceptible microorganisms may occur as with other antibacterial agents.

#### Immune mediated haemolytic anaemia

Immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials. 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 a cephalosporin-associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

#### 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 milligram weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

During prolonged treatment the blood profile should be checked at regular intervals.

#### Interactions with calcium-containing products

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and calcium-containing IV solutions in patients other than neonates. Therefore, ceftriaxone and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient

irrespective of age, even via different infusion lines at different sites.

As a further theoretical consideration and based on 5 half-lives of ceftriaxone, calcium- containing IV solutions and ceftriaxone should not be administered within 48 hours of each other, in any patient.

No data are available on the potential interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

#### Others

Ceftriaxone should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

Pseudomembranous colitis and delaying peristalsis-Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop diarrhoea in association with the use of ceftriaxone. Drugs which delay peristalsis may prolong and/or worsen the condition and should not be used.

Prolonged prothrombin time may occur in patients receiving protracted antimicrobial therapy.

Shadows which have been 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 calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy. Rarely have these findings been associated with symptoms. In asymptomatic cases discontinuation of treatment is not recommended as the condition is reversible after completion of the treatment. In symptomatic cases, conservative non-surgical management is recommended. Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the clinician.

Pancreatitis, possibly of biliary obstruction aetiology, has been rarely 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 cannot be discounted.

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described in section 4.2. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Caution should be exercised when considering ceftriaxone for hyperbilirubinaemic neonates, especially prematures. Ceftriaxone should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy.

#### **4.5 Interaction with other medicines and other forms of interaction**

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

There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides.

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

The elimination of ceftriaxone is not altered by probenecid.

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

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

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

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Category B1

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive toxicity studies have been performed in mice and rats at doses up to 20 times the human dose of 2 g/d (586 mg/kg/d in rats), and have not shown evidence of embryotoxicity, foetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or peri- and postnatal development. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose (84 mg/kg/d in monkeys).

##### Breast-feeding

As ceftriaxone is secreted in the breast milk at low concentrations, caution is advised in nursing mothers.

#### **4.7 Effects on ability to drive and use machines**

During treatment with ceftriaxone undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

#### **4.8 Undesirable effects**

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

### Systemic side effects

Gastrointestinal complaints (about 2% of cases): loose stools or diarrhoea, nausea, vomiting, stomatitis and glossitis.

Haematological changes (about 2%): eosinophilia, leukopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia.

Skin reactions (about 1%): exanthema, allergic dermatitis, pruritus, urticaria, oedema, erythema multiforme.

Other, rare side effects: headache and dizziness, increase in liver enzymes, jaundice and hepatitis, symptomatic precipitation of the calcium salt of ceftriaxone in the gallbladder, oliguria, increase in serum creatinine, mycosis of the genital tract, shivering and anaphylactic or anaphylactoid reactions and secondary infection.

Pseudomembranous enterocolitis and coagulation disorders have been reported as very rare side effects. Pancreatitis and Steven Johnson Syndrome have also been reported as very rare side effects.

Very rare cases of renal precipitation have been reported, mostly in children aged 3 years or older, who have been treated with high doses (> 80 mg/kg/day) or total doses of greater than 10 g and presenting other risk factors (e.g. fluid restrictions, confinement to bed, etc.). This may be symptomatic or asymptomatic, may lead to renal insufficiency and is reversible with discontinuation of ceftriaxone.

Fatal reactions with calcium-ceftriaxone precipitates in lungs and kidney 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.

### Local side effects

Phlebitis at the site of injection and cutaneous vasculitis may occur. These may be minimized by slow (two to four minutes) injection of the substance.

Intramuscular injection without lidocaine solution is painful.

### 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://nzphvc.otago.ac.nz/reporting/>

## **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 overdose should be symptomatic.

For 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

Ceftriaxone is a long acting, broad-spectrum cephalosporin antibiotic for parenteral use. The bactericidal activity of ceftriaxone results from inhibition of 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 beta-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 section 4.1):

#### *Gram-positive aerobes:*

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

#### NOTE:

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

#### *Gram-negative aerobes:*

- *Acinetobacter lwoffii*
- *Acinetobacter anitratus* (mostly *A. baumannii*)\*
- *Aeromonas hydrophila*
- *Alcaligenes faecalis*
- *Alcaligenes odorans*
- *Alcaligenes*-like bacteria
- *Borrelia burgdorferi*

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- *Capnocytophaga* spp.
  - *Citrobacter diversus* (including *C. amalonaticus*)
  - *Citrobacter freundii*\*
  - *Escherichia coli*
  - *Enterobacter aerogenes*\*
  - *Enterobacter cloacae*\*
  - *Enterobacter* spp. (other)
  - *Haemophilus ducreyi*
  - *Haemophilus influenza*
  - *Haemophilus parainfluenzae*
  - *Hafnia alvei*
  - *Klebsiella oxytoca*
  - *Klebsiella pneumoniae*\*\*
  - *Moraxella catarrhalis* (former *Branhamella catarrhalis*)
  - *Moraxella osloensis*
  - *Moraxella* spp. (other)
  - *Morganella morganii*
  - *Neisseria gonorrhoeae*
  - *Neisseria meningitides*
  - *Pasteurella multocida*
  - *Plesiomonas shigelloides*
  - *Proteus penneri*\*
  - *Proteus mirabilis*
  - *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  $\beta$ -lactamase.

\*\*Some isolates of these species are resistant due to production of extended spectrum plasmid mediated  $\beta$ -lactamase.

**NOTE:**

Many strains of the above microorganisms that are multiple resistant to other antibiotics, e.g. amino- 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 the *C. difficile*)
- *Fusobacterium nucleatum*
- *Fusobacterium* spp. (other)
- *Gaffkia anaerobica* (former *Peptococcus*)
- *Peptostreptococcus* spp.

\*Some isolates of these species are resistant to ceftriaxone due to  $\beta$ -lactamase-production.

**NOTE:**

Many strains of  $\beta$ -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 standardised techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued interpretative breakpoints for ceftriaxone are:

	Susceptible	Moderately susceptible	Resistant
Dilution test, inhibitory concentrations in mg/L	$\leq 8$	16-32	$\geq 32$
Diffusion test (disk with 30 $\mu$ g ceftriaxone), inhibition zone diameter in mm	$\geq 21$	20-14	$\leq 13$

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 standardised, susceptibility interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

## 5.2 Pharmacokinetic properties

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. An overall mean and the range of means from studies have been presented for the primary pharmacokinetic parameters of ceftriaxone administered in the dose range 150 mg – 3 g.

### Absorption

The maximum plasma concentration after a single IM 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 IM administration is equivalent to that after IV 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.

Following intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, sustaining bactericidal concentrations against susceptible organisms for 24 hours.

### *Protein binding*

Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in the 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.

### *Penetration into particular tissues*

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children. Ceftriaxone concentrations are >1.4 mg/L in the CSF 24 hours after IV injection of Ceftriaxone in doses of 50 – 100 mg per kg (neonates and infants, respectively). Peak concentration in CSF is reached about 4 hours after IV injection and gives an average value of 18 mg/L. The average extent of diffusion into the cerebrospinal fluid during bacterial meningitis is 17% of the plasma concentration and 4% in patients with aseptic meningitis. In adult meningitis patients, administration of 50 mg per kg leads within 2 – 24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common causative organisms of meningitis.

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

### Metabolism

Ceftriaxone is not metabolized systemically; only the intestinal flora transforms the agent into inactive metabolites.

### Elimination

The 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 eight hours.

**Special populations***Neonates and elderly patients*

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 to 3 times that in the young adult group.

*Renal or hepatic dysfunction*

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.

**5.3 Preclinical safety data**

Repeated dose administrations in animals revealed the known and reversible side effect of parenterally administered third-generation cephalosporins at high doses (e.g. alteration of laboratory parameters, enteric disturbances and a certain degree of nephrotoxicity). A specific side effect of ceftriaxone is the formation of biliary calculi in the gallbladder of dogs, and to a minor extent in monkeys. Ceftriaxone had no effect on reproductive parameters, and was found to have neither mutagenic nor antigenic activity.

**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 ampicillin, vancomycin and fluconazole and aminoglycosides.

**6.3 Shelf life**

Powder: 36 months.

Reconstituted solution: 24 hours when stored in a refrigerator (2 – 8°C). Do not freeze. Protect from light.

**6.4 Special precautions for storage**

Store below 25°C. Protect from light.

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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% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl starch 6-10% infusions, sterile water for injections.

Ceftriaxone 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.

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

## **7. MEDICINE SCHEDULE**

Prescription Medicine.

## **8. SPONSOR**

AFT Pharmaceuticals Ltd

PO Box 33-203  
Takapuna  
Auckland 0740  
Phone: 0800 423 823

## **9. DATE OF FIRST APPROVAL**

13 January 2011

## **10. DATE OF REVISION OF THE TEXT**

28 July 2020

Summary table of changes:

<b>Section changed</b>	<b>Summary of new information</b>
All	Reformat.
4.2	Intramuscular method of administration for Ceftriaxone-AFT 500 mg added.