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

Considerations should be given to local guidelines on appropriate use of antibacterial agents.

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. Twice daily (12 hourly) administration may be considered where doses greater than 2g daily are administered.

Specific dosage schedules

Gonorrhoea

For the treatment of gonorrhoea (penicillinase-producing and non-penicillinase-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.

Paediatric population

Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks gestational age + chronological age) and in full term neonates (up to 28 days of age) with hyperbilirubinemia, jaundice, or who are hypoalbuminemia or acidotic, because these are conditions where bilirubin binding is likely to be impaired, or if they require (or expected to require) intravenous calcium treatment or calcium-containing infusions due to the risk of precipitation of ceftriaxone -calcium salt (see section 4.3 and 4.4).

The following dosage schedules are recommended for once daily administration.

Neonates (up to 14 days old): A daily dose of 20-50 mg/kg bodyweight, depending on the severity of the infection, not to exceed 50 mg/kg, on account of the immaturity of the infant's enzyme systems. A dose of 50mg/kg is generally recommended in treatment of meningitis.

Neonates, infants, and children (15 days to 12 years old who are < 50Kg): A daily dose of 20-80 mg/kg, depending on the severity of the infection.

NOTE: For children with bodyweights of 50 kg or more, the usual adult dosage should be used (see above).

Special dosage instructions

In bacterial meningitis in infants and children (aged 15 days to 12 years old who are < 50Kg) 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.

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.

Use in hepatic impairment

Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.

Use in renal impairment

A maximum dose of 2g daily is recommended if creatinine clearance is < 10 mL/min.

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.

Use in renal and hepatic impairment

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. Close clinical monitoring for safety and efficacy is advised.

Elderly patients

The dosages recommended for adults require no modification in the case of geriatric patients. provided that renal and hepatic function is not impaired.

Paediatric use

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described in section 4.2.

Ceftriaxone should not be given to neonates who may be at risk of developing bilirubin encephalopathy. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone is contraindicated in premature and full-term neonates with conditions that may increase the risk of developing bilirubin encephalopathy (see section 4.3, 4.4).

Ceftriaxone is also contraindicated in neonates who require or are expected to require treatment with calcium containing IV solutions, including parenteral nutrition, due to risk of precipitation of a ceftriaxone-calcium salt (see section 4.3, 4.4).

Method of administration

Ceftriaxone can be administered by intravenous infusion, intravenous injection, or intramuscular injection.

Ceftriaxone must be reconstituted prior to use. For instructions on reconstitution of the medicine before administration, see section 6.6.

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.

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, ceftriaxone and calcium containing solutions must not be mixed or administered simultaneously (see section 4.4).

Intramuscular injection

Intramuscular administration may be considered when the intravenous route is not possible or less appropriate for the patient.

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. For doses greater than 2g, intravenous administration should generally be used.

The lidocaine solution must never be administered intravenously.

Refer to the information in the lidocaine data sheet (see section 4.4)

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 doses for neonates, infants, and children under 12 years of age should be given by infusion.

Intravenous infusion

The infusion should be administered over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

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.

The infusion line should be flushed after each administration.

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. (See section 4.4)

Premature neonates up to a postmenstrual age of 41 weeks (weeks of gestation + weeks of life) *

Full term neonates (up to 28 days of age) with hyperbilirubinemia, jaundice, or who are hypoalbuminemia or acidotic, because these are conditions where bilirubin binding is likely to be impaired*

Full term neonates (up to 28 days of age) if they require (or expected to require) intravenous calcium treatment or calcium-containing infusions due to the risk of precipitation of ceftriaxone - calcium salt (see section 4.4).

*in vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before starting treatment, careful inquiry should be made to determine whether the patient has had previous severe hypersensitivity reactions to ceftriaxone, cephalosporins, penicillin or other beta-lactam antibiotics.

Ceftriaxone is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to cephalosporin or penicillin. Ceftriaxone should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin, or other beta-lactam antibiotics. Specialist advice and local guidelines should be consulted.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Hypersensitivity reactions may occur in susceptible individuals. If a severe allergic reaction occurs during treatment, the medicine should be discontinued, and appropriate measures taken.

Severe cutaneous adverse reactions (SCAR) (Stevens Johnson syndrome or toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be life-threatening or fatal have been reported in association of ceftriaxone treatment. When SCAR is suspected, treatment should be discontinued, and appropriate measures taken. An alternative treatment should be considered.

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.

Overgrowth of other non-susceptible organisms

Prolonged use of antibiotics may result in overgrowth of non-susceptible organisms.

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

If superinfection occurs during therapy, appropriate measures should be taken.

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 may be necessary if the prothrombin time is prolonged before or during therapy.

Interactions with calcium-containing products

In neonates, 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. Ceftriaxone is contraindicated in neonates if they require (or are expected to require) intravenous calcium treatment or calcium-containing infusions due to the risk of precipitation (see section 4.3). Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described. In some cases, the infusion lines, and the times of administration of ceftriaxone and calcium-containing solutions differed.

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.

In patients of any age, ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusions sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, and the infusion flushed between solutions.

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).

Gall bladder precipitates

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. Caution should be particularly considered in the paediatric population.

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.

Precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. 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

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.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

Risk of bilirubin encephalopathy in neonates

In vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone is contraindicated premature neonates up to a postmenstrual age of 41 weeks (weeks of gestation + weeks of life) and in full term neonates (up to 28 days of age) with hyperbilirubinemia, jaundice, or who are hypoalbuminemia or acidotic (conditions where bilirubin binding is likely to be impaired) due to the risk of developing bilirubin encephalopathy (see section 4.3).

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, 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.

Use of lidocaine

In case a lidocaine solution is used as a solvent, ceftriaxone solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as detailed in the data sheet should be considered before use. The lidocaine solution should never be administered intravenously.

History of gastro-intestinal disease

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

Long term treatment

Haematological changes such as eosinophilia, leukopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia and isolated cases of agranulocytosis have been reported, mostly after 10 days of treatment at higher doses.

During prolonged treatment the completed blood counts should be done at regular intervals.

Antibacterial spectrum

Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed. In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Severe renal and hepatic insufficiency

In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised (see section 4.2).

In adult patients with both hepatic impairment and significant renal disease, the dose should not exceed 2g daily.

Effects of laboratory tests

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

Non-enzymatic 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.

4.5 Interaction with other medicines and other forms of interaction

Calcium-containing diluents

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous 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 have an increased risk of precipitation of ceftriaxone-calcium.

Use with oral anticoagulants.

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently, and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone.

Diuretics

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

Aminoglycosides

There is conflicting evidence that ceftriaxone increases renal toxicity of aminoglycosides. Monitoring of aminoglycosides levels and renal function should be followed.

Alcohol

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.

Probenecid
The elimination of ceftriaxone is not altered by probenecid.

Chloramphenicol
In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

4.6 Fertility, pregnancy, and lactation

Pregnancy
Category B1
Ceftriaxone crosses the placental barrier.
There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal, and postnatal development (see section 5.3).

Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

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

However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Reproductive studies have shown no evidence of adverse effects on male or female fertility.

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

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

The following convention has been used for the classification of frequency:
Very common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1000 - < 1/100)
Rare (≥ 1/10000 - < 1/1000)
Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not Known [a]
Infections and infestations		Genital fungal infection	Pseudo-membranous colitis[b]	Superinfection[b]

Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b]
Nervous system disorders		Headache Dizziness	Encephalopathy	Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic, and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation [b] Kernicterus Hepatitis [c] Hepatitis cholestatic [b,c]
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome [b] Toxic epidermal necrolysis [b] Erythema multiforme Acute generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS) [b]
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site reactions Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive [b] Galactosaemia test false positive [b] Non enzymatic methods for glucose determination false positive [b]

[a] Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

[b] See section 4.4

[c] Usually reversible upon discontinuation of ceftriaxone

Description of selected adverse reactions

Ceftriaxone is generally well tolerated.

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with Clostridium difficile. Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation

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. The high risk of precipitation in neonates is a result of their

low blood volume and the longer half-life compared with adults (see section 4.4)

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. (See section 4.4)

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose (see section 4.4).

Injection site reactions
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. In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. There is no specific antidote. Treatment of overdosage 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* (β-hemolytic, group A)
- *Streptococcus agalactiae* (β-hemolytic, group B)
- *Streptococci* β-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 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 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**
- *Psudomonas* 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 β-lactamase.
**Some isolates of these species are resistant due to production of extended spectrum plasmid mediated β-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. difficle*)
- *Fusobacterium nucleatum*
- *Fusobacterium* spp. (other)
- *Gaffkia anaerobica* (former *Peptococcus*)
- *Peptostreptococcus* spp.

*Some isolates of these species are resistant to ceftriaxone due to β-lactamase-production.

NOTE:
Many strains of β-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	≤ 8	16-32	≥ 32
Diffusion test (disk with 30 µg ceftriaxone), inhibition zone diameter in mm	≥ 21	20-14	≤ 13

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

Where NCCLS recommendations are not in daily use, alternative, well 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 concentration 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.

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, fetotoxicity, 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).

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.

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.

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

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9. DATE OF FIRST APPROVAL

13 January 2011

10. DATE OF REVISION OF THE TEXT

03 July 2023

Summary table of changes:

Section changed	Summary of new information
4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.3	Safety Update