CEFTRIAXONE-AFT

Ceftriaxone sodium equivalent to ceftriaxone 500 mg, 1 g and 2 g powder for injection

1. Presentation

Ceftriaxone-AFT is a white to pale yellow powder packed in vials which contain the equivalent of 500 mg, 1 g or 2 g ceftriaxone.

2. Uses

1. Actions

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 Indications):

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 influenzae
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella oxytoca
*Klebsiella pneumoniae***
*Moraxella catarrhalis (*former*Branhamella catarrhalis)*
Moraxella osloensis
Moraxella spp. (other)
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
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. difficile*)
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	≥64
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.

2. Pharmacokinetics

Ceftriaxone is a long acting, broad-spectrum cephalosporin antibiotic for parenteral use. Ceftriaxone inhibits the bacterial cell wall synthesis leading to lysis of bacteria.

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.

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; and cerebrospinal, pleural, prostatic and synovial fluids.

On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.

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.

Pharmacokinetics in special clinical situations:

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. 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.

Preclinical safety data:

Teratogenicity

Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed.

3. Indications

Infections caused by pathogens sensitive to Ceftriaxone e.g.:

- o sepsis;
- o meningitis;
- o abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);
- o infections of the bones, joints, soft tissue, skin and of wounds;
- o infections in patients with impaired defence mechanisms;
- o renal and urinary tract infections;
- o respiratory tract infections, particularly pneumonia, and ear, nose and throat infections;
- o genital infections, including gonorrhoea.

Perioperative prophylaxis of infections.

3. Dosage and administration

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.

Ceftriaxone must not be administered simultaneously with calcium-containing IV 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 (see Interactions with Calcium-Containing Products).

1. 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.

2. Elderly patients:

The dosages recommended for adults require no modification in the case of elderly patients, provided there is no severe renal and hepatic impairment.

3. Neonates, Infants and Children up to twelve years:

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

NOTE:

4. Intravenous doses of ≥50 mg/kg bodyweight, in infants and children up to 12 years of age, should be given by infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy. 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.

5. 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.

6. 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 meningitidis	4 days
Haemophilus influenzae	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.

7. Directions for 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 25°C 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.

Intramuscular injection:

For IM injection, 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 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 is dissolved in 40 mL of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, 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. Contraindications

Hypersensitivity

Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone or to the cephalosporin class of antibiotics. In patients hypersensitive to penicillin and other beta lactam agents, the possibility of allergic cross-reactions should be borne in mind.

Hyperbilirubinemic newborns

Ceftriaxone is contraindicated in hyperbilirubinemic newborns 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.

Lidocaine

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent (see section 2.2 Dosage and Administration). See contraindications section in the prescribing information of lidocaine. Ceftriaxone solutions containing lidocaine should never be administered intravenously.

Premature Neonates

Ceftriaxone-AFT is contraindicated in premature neonates up to postmenstrual age of 41 weeks (gestational age + chronological age)

Neonates and Calcium Containing IV Solutions.

Ceftriaxone is contraindicated in neonates (≤28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see Dosage and administration and Interactions with Calcium-Containing Products).

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 intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

5. Warnings and precautions

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 a cephalosporin associated anaemia should be considered and ceftriaxone discontinued until the etiology is determined.

Hypersensitivity

Hypersensitivity reactions may occur in susceptible individuals.

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of hypersensitivity reactions to ceftriaxone, to other cephalosporins, or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of hypersensitivity to other beta-lactam agents.

Clostridium difficile associated diarrhoea (CDAD)

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 of 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 antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the 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 evaluation should be instituted as clinically indicated.

Superinfections

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

Calcium-ceftriaxone precipitates

Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving ceftriaxone, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in paediatric patients. Precipitates disappear after discontinuation of ceftriaxone therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of ceftriaxone treatment should be considered by the physician based on an individual benefit-risk assessment.

In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. However, ceftriaxone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines. As a theoretical consideration and based on 5 half-lives of ceftriaxone (at which point negligible amounts of the original ceftriaxone dose would be present), ceftriaxone and IV calcium-containing solutions should not be administered within 5 days of each other in neonates and in infants up to 10 weeks of age (by ten weeks of age the ceftriaxone half-life is generally less than 10 hours).

Pancreatitis

Pancreatitis possibly of biliary obstruction aetiology have 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.

Paediatrics

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

Blood Monitoring

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

1. Interactions with Calcium-Containing Products

In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. However, ceftriaxone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines. As a theoretical consideration and based on 5 half-lives of ceftriaxone (at which point negligible amounts of the original ceftriaxone dose would be present), ceftriaxone and IV calcium-containing solutions should not be administered within 5 days of each other in neonates and in infants up to 10 weeks of age (by ten weeks of age the ceftriaxone half-life is generally less than 10 hours).

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).

2. Pregnancy and Lactation:

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).

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

3. 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.

6. Adverse effects

Clinical Trials

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

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

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)

Table 1 Tabulated List of Adverse Reactions

System Organ Class	Common	Uncommon	Rare
Infections and Infestations		Genital fungal infection	Pseudo-membranous colitis
Blood and lymphatic system disorders	Eosinophilia Leucopoenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy	
Nervous system disorders		Headache Dizziness	
Respiratory, thoracic and mediastinal disorders			Bronchospasm
Gastrointestinal disorders	Diarrhoea Loose stools	Nausea Vomiting	
Hepatobiliary disorders	Hepatic enzyme increased		
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria
Renal and urinary disorders			Haematuria Glycosuria
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema
Investigations		Blood creatinine increased	

Post Marketing

The following adverse reactions have been identified during post-marketing use of Ceftriaxone-AFT. These reactions are reported from a population of uncertain size, therefore, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure.

Systemic side effects

Gastrointestinal complaints: pancreatitis, stomatitis and glossitis.

Haematological changes: Isolated cases of agranulocytosis (<500/mm3) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Skin reactions: Acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson syndrome or Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Nervous system disorders: convulsion

Infections and Infestations: superinfection

Other, rare side effects

Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

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 interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

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-AFT and calcium containing fluids. In some of these cases, the same intravenous infusion line was used for both Ceftriaxone-AFT and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Ceftriaxone-AFT and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see 2.4.1 Warnings and Precautions, General).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure but is usually reversible upon discontinuation of Ceftriaxone-AFT.

Local side effects

In rare cases, phlebitis reactions occurred after i.v. administration. These may be minimized by slow (2-4 minutes) injection.

Investigations: Coombs test false positive, galactosemia test false positive, non-enzymatic methods for glucose determination false positive.

7. Interactions

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 conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels and renal function in clinical practice should be closely adhered to in such cases. 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 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.

Concomitant use of ceftriaxone with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone.

8. Overdosage

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.

9. Pharmaceutical precautions

1. Incompatibilities:

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 powder for injection should be stored at or below 30 °C and protected from light.

Instructions for use/handling:

Ceftriaxone powder must be reconstituted prior to use

Reconstituted solutions retain their physical and chemical stability for six hours at 25°C (or 24 hours at 2-8 °C).

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 is dissolved in 40 mL of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl starch 6-10% infusions, sterile water for injections.

10. Medicine classification

Prescription Medicine.

11. Package quantities

Ceftriaxone-AFT 500 mg, 1 g and 2 g are available in:
Single vial packs
Packs of 5 vials
Packs of 10 vials.

12. Further information

Ceftriaxone sodium 0.540g equivalent to Ceftriaxone 0.5g.
Ceftriaxone sodium 1.079g equivalent to Ceftriaxone 1g.
Ceftriaxone sodium 2.159g equivalent to Ceftriaxone 2g.
Ceftriaxone-AFT contains approximately 83mg (3.6m Eq) of sodium per gram of ceftriaxone.
Store below 30°C. Do not refrigerate or freeze. Store in the outer carton in order to protect from light.

13. Product Owner

AFT Pharmaceutical Ltd
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14. Date of preparation

Dec 2018 v1