

NEW ZEALAND DATA SHEET

CEFTRIAXONE PFIZER®

Generic Name

Ceftriaxone sodium

Dose form and Strength

0.5 g, 1 g and 2 g powder for injection

PRESENTATION

CEFTRIAXONE PFIZER ceftriaxone sodium for injection 0.5 g

White to yellowish crystalline powder filled in 15 ml moulded Type-I clear glass vials with 20 mm bromo butyl rubber stoppers sealed with 20 mm aluminium seal having cream colour PP disc.

CEFTRIAXONE PFIZER ceftriaxone sodium for injection 1 g

White to yellowish crystalline powder filled in 15 ml moulded Type-I clear glass vials with 20 mm bromo butyl rubber stoppers sealed with 20 mm aluminium seal having yellow colour PP disc.

CEFTRIAXONE PFIZER ceftriaxone sodium for injection 2 g

White to yellowish crystalline powder filled in 50 ml moulded Type-I clear glass vials with 32 mm bromo butyl rubber stoppers sealed with 33 mm aluminium seal having lemon yellow colour PP disc.

USES

Actions

Ceftriaxone is a long acting, broad-spectrum cephalosporin antibiotic for parenteral use. The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis. Ceftriaxone exerts *in vitro* activity against a wide range of Gram-negative and Gram-positive micro-organisms. Ceftriaxone is highly stable to most β -lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria.

Ceftriaxone is usually active against the following micro-organisms *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 lwoffii,
Acinetobacter anitratus (mostly *A. baumannii*)*,
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 gonorrhoea,
Neisseria meningitidis,
Pasteurella multocida,
Plesiomonas shigelloides,
Proteus mirabilis,
Proteus penneri *,
Proteus vulgaris *,
Pseudomonas cepacia
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 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 micro-organisms that are multiple resistant to other antibiotics, e.g. amino-penicillins 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. *Borrelia burgdorferi* can also be classified as highly sensitive to ceftriaxone, according to the available *in vitro* and *in vivo* data. With a few exceptions clinical *P. aeruginosa* isolates are resistant to ceftriaxone.

Anaerobic organisms

Bacteroides spp. (bile-sensitive)*,
Clostridium spp. (excluding *C. perfringens* group),
Fusobacterium nucleatum,
Fusobacterium spp. (other),
Gaffkia anaerobica (formerly *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 the following interpretative breakpoints for ceftriaxone:

	Susceptible	Moderately susceptible	Resistant
<u>Dilution test</u> inhibitory concentrations in mg/L	≤ 8	16-32	≥ 64
<u>Diffusion test</u> (disk with 30 μ g ceftriaxone), inhibition zone diameter in mm	≥ 21	20-14	≤ 13

Micro-organisms 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.

Pharmacokinetics

The pharmacokinetics of ceftriaxone are non-linear 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 0.15-3 g.

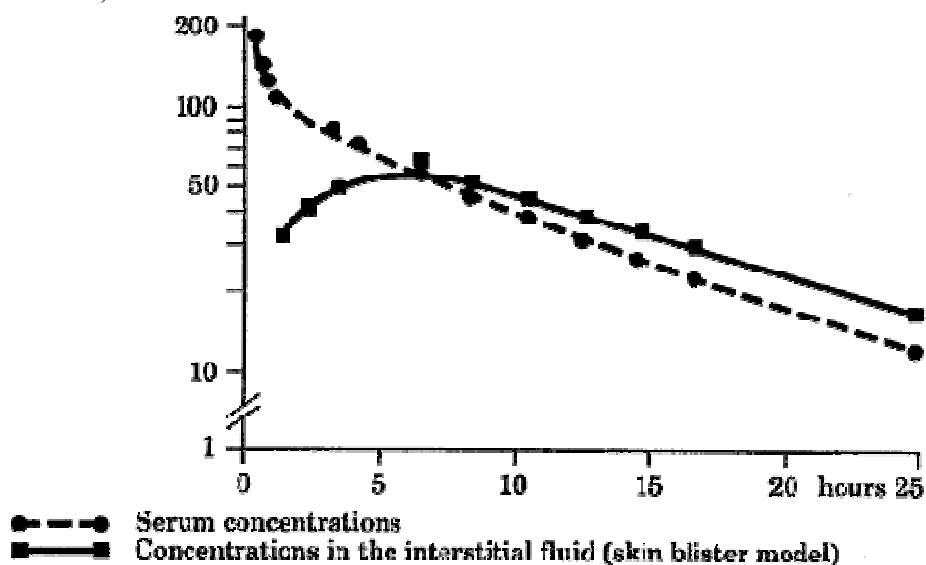
Absorption

The maximum plasma concentration after a single *i.m.* 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 *i.m.* administration is equivalent to that after *i.v.* 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.

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



Protein binding

Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration, e.g. from 95% binding at plasma concentrations of <100 mg/L to 85% binding at 300 mg/L. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Penetration into particular tissues

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children: Ceftriaxone concentrations exceed 1.4 mg/L in the Cerebrospinal Fluid (CSF) 24 hours after *i.v.* injection of ceftriaxone in doses of 50-100 mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after *i.v.* 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 plasma concentrations and 4% in patients with aseptic meningitis.

In adult meningitis patients, administration of 50 mg/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 metabolised systemically; but is converted to inactive metabolites by the intestinal flora.

Elimination

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 8 hours.

Pharmacokinetics in special clinical situations

In neonates, urinary recovery accounts for about 70% of the dose. In infants aged less than 8 days and in elderly persons aged over 75 years the average elimination half-life is usually two to three times that in young adults.

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:

Repeated dose administrations in animals revealed the known and reversible side effect of parenterally administered 3rd-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, also in monkeys. Ceftriaxone had no effect on reproductive parameters, and was found to have neither mutagenic nor antigenic activity.

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.

DOSAGE AND ADMINISTRATION

Dosage

Ceftriaxone Pfizer may be administered intravenously or intramuscularly. The recommended adult daily dose is 1 to 2 g given once a day or in equally divided doses twice a day depending on the type and severity of the infection. The lower dose would be appropriate for less severe infections. In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, administered once daily.

For the treatment of uncomplicated gonococcal infections a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis) in cardiovascular surgery, biliary tract surgery in high risk patients and in vaginal and abdominal hysterectomy a single dose of 1 g administered ½ to 2 hours before surgery is recommended.

For the treatment of serious miscellaneous infections in children, the recommended total daily dose is 50-75 mg/kg (not to exceed 2 grams), given once per day or in divided doses every 12 hours. In meningitis the dose should be divided and administered every twelve hours.

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

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

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

Administration

The product is for one dose in one patient only. Discard any remaining contents.

The use of freshly prepared solutions is recommended. These retain their efficacy for at least six hours at room temperature (or 24 hours at 5 °C). The solutions are yellowish in colour; this characteristic of the active ingredient is of no significance to the efficacy or tolerance of the drug. A slight opalescence may be seen in the reconstituted solution.

Ceftriaxone Pfizer should not be added to solutions containing calcium such as Hartmann's solution and Ringer's solution. Ceftriaxone Pfizer should also not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed below, owing to possible incompatibility. Specifically, the literature reports that ceftriaxone is incompatible with amsacrine, vancomycin and fluconazole and aminoglycosides.

Intramuscular injection: Ceftriaxone Pfizer 0.5 g is dissolved in 2.0 mL, or Ceftriaxone Pfizer 1 g is dissolved in 3.5 mL of 1% lignocaine solution, and administered by deep intragluteal injection. It is recommended that no more than 1 g be injected on either side.

The lignocaine solution must never be administered intravenously.

Ceftriaxone Pfizer should be injected well into the body of a relatively large muscle mass. Intramuscular injection of Ceftriaxone Pfizer without lignocaine solution is painful.

Intravenous injection: Ceftriaxone Sodium 0.5 g is dissolved in 5 mL, or Ceftriaxone Pfizer 1 g is dissolved in 10 mL of water for injection, and then administered by direct intravenous injection lasting two to four minutes.

Intravenous infusion: Two grams of Ceftriaxone Pfizer are dissolved in approximately 40 mL of one of the following infusion solutions:

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

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

Use in the Elderly

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

CONTRAINDICATIONS

Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone or the excipients or to the cephalosporin class of antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind. Although the relevant preclinical investigations revealed neither mutagenic nor teratogenic effects, ceftriaxone should not be used in pregnancy (particularly in the first trimester) unless absolutely indicated.

Hyperbilirubinemic Neonates:

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.

Neonates (≤28 days)

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.

(see WARNINGS and PRECAUTIONS: Calcium-containing Solutions and ADVERSE EFFECTS)

WARNINGS AND PRECAUTIONS

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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

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

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 nonsurgical management is recommended.

Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician.

Cases of 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 cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described under Dosage and Administration section. *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 (see CONTRAINDICATIONS).

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

Calcium-containing Solutions:

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion 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 (see CONTRAINDICATIONS for information regarding newborns).

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, considering the advice to flush infusion lines between solutions.

Pregnancy and Lactation

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive toxicity studies 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 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 was demonstrated at a dose approximately 3 times the human dose (84 mg/kg/d in monkeys).

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

Effects on ability to drive and use machinery

There are no data to indicate any effect on a person's ability to drive or use machines.

ADVERSE 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 the cases): loose stools or diarrhea, nausea, vomiting, stomatitis and glossitis.

Hematological changes (about 2%): eosinophilia, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia. Isolated cases of agranulocytosis ($< 500/\text{mm}^3$) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Skin reactions (about 1%): exanthema, allergic dermatitis, pruritus, urticaria, edema. Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson syndrome or Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

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

Pseudomembranous enterocolitis and coagulation disorders have been reported as very rare side effects.

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

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung 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

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

Intramuscular injection *without* lidocaine solution is painful.

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 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.

Laboratory Tests

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

Likewise, 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.

Calcium-containing Solutions:

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion 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 (see CONTRAINDICATIONS for information regarding newborns).

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, considering the advice to flush infusion lines between solutions.

OVERDOSAGE

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

PHARMACEUTICAL PRECAUTIONS

Instructions for Use/Handling

Ceftriaxone powder must be reconstituted prior to use (see DOSAGE AND ADMINISTRATION).

Dry Powder: Store below 30 °C. Protect from Light

Reconstituted Solution: Store at 25 °C for a maximum of 6 hours or at 2-8 °C (refrigerate, do not freeze) for a maximum of 24 hours.

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.

Shelf life

24 months.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

For intramuscular or intravenous injection:

CEFTRIAZONE PFIZER (Ceftriaxone as sodium) 0.5 g* and 1 g are presented in 1 vial, 5 vial and 10 vial* packs.

For intravenous infusion:

CEFTRIAZONE PFIZER (Ceftriaxone as sodium) 2 g are presented in 1 vial pack.

* not marketed

FURTHER INFORMATION

Ceftriaxone sodium is almost white or yellowish, crystalline powder and slightly hygroscopic.

The chemical name of Ceftriaxone sodium is:

Disodium (6R,7R)-7-[[*Z*-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[*Z*-(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphonyl]methyl]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate.

Ceftriaxone sodium is freely soluble in water, sparingly soluble in methanol, very slightly soluble in ethanol, and has a molecular weight of 662.

NAME AND ADDRESS

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DATE OF PREPARATION

22 July 2011