

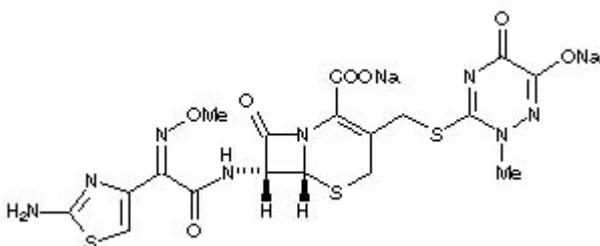
PRODUCT INFORMATION

CEFTRIAXONE SANDOZ 1g/2g POWDER FOR INJECTION

NAME OF THE MEDICINE

Generic name: Ceftriaxone sodium

Chemical structure:



$3\frac{1}{2}\text{H}_2\text{O}$

Chemical name:

disodium(Z)-(6R,7R)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino)acetamido]-8-oxo-3-[(2,5-dihydro-2-methyl-6-oxido-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate hemiheptahydrate

Molecular formula: $\text{C}_{18}\text{H}_{16}\text{N}_8\text{Na}_2\text{O}_7\text{S}_3 \cdot 3\frac{1}{2}\text{H}_2\text{O}$

Molecular weight: 662

CAS: 104376-79-6

DESCRIPTION

It is an almost white to yellowish crystalline powder which is slightly hygroscopic, very soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 5% aqueous solution is approximately 6 to 8. The colour of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used. Ceftriaxone sodium contains approximately 83mg (3.6mEq) of sodium per g of ceftriaxone activity. Ceftriaxone Sandoz powder for injection contains ceftriaxone sodium as a single ingredient.

PHARMACOLOGY

Semisynthetic broad spectrum cephalosporin antibiotic.

Microbiology

The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases (types I, II and III), both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria. It is susceptible to type IV beta-lactamases at approximately 18% of the rate of cephaloridine. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see INDICATIONS).

Gram-negative aerobes: *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae* (including ampicillin resistant strains), *Klebsiella* sp. (including *K. pneumoniae*); *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *N. meningitidis*, *Proteus mirabilis*, *P. vulgaris*, *Morganella morganii* and *Serratia marcescens*.

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

Gram-positive aerobes: *Staphylococcus aureus* (including penicillinase producing strains) and *Staph. epidermidis* (methicillin resistant *Staphylococci* are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (group A beta-haemolytic *Streptococci*), *Strep. agalactiae* (group B *Streptococci*) and *Strep. pneumoniae*, group G *Streptococci*, *Strep. viridans* and *Streptococcus* sp. (Most species of group D *Streptococci* including *Strep. faecalis* and *Strep. faecium* are resistant.)

Susceptibility testing

Standard susceptibility disc method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (the Bauer Kirby Sherris Turck method) has been recommended for use with discs to test susceptibility to ceftriaxone.¹⁻³

Laboratory results of the standardised single disc susceptibility test using a ceftriaxone 30 microgram disc should be interpreted according to the following three criteria.

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

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

Standardised procedures require the use of control organisms. The ceftriaxone 30 microgram disc should give zone diameters between 29 and 35mm, 22 and 28mm, and 17

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and 23mm for the reference strains *E. coli* ATCC 25922, *Staph. aureus* ATCC 25923 and *Ps. aeruginosa* ATCC 27853, respectively.

Dilution techniques

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

1. Bauer AW, Kirby WMM, Sherris JC, Turck M. *Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol* 1966; 45: 493-96.
2. Standardized Disk Susceptibility Test. Federal Register 1974; 39: 19182-84.
3. National Committee for Clinical Laboratory Standards Approved Standard: ASM-2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975.

Pharmacokinetics

Ceftriaxone is poorly absorbed from the gastrointestinal tract. Average plasma concentrations of ceftriaxone following a single 30 minute intravenous (IV) infusion of a 0.5, 1 or 2g dose and intramuscular (IM) administration of a single 0.5 or 1g dose in healthy subjects are presented in Table 1.

Table 1. Average ceftriaxone plasma concentrations (mcg/mL) after a single dose administration.

Dose	Route	Time after dose (hours)								
		0.5	1	2	4	6	8	12	16	24
0.5g	IV	82	59	48	37	29	23	15	10	5
0.5g	IM	30	41	43	39	31	25	16	ND	ND
1.0g	IV	151	111	88	67	53	43	28	18	9
1.0g	IM	40	68	76	68	56	44	29	ND	ND
2.0g	IV	257	192	154	117	89	74	46	31	15

IV doses were infused at a constant rate over 30 minutes

IM doses were administered with lignocaine

ND = not determined

Mean maximum plasma concentrations following IM injection occurred between two and three hours postdosing. Multiple IV or IM doses ranging from 0.5 to 2g at 12 to 24 hour intervals resulted in 15 to 36% accumulation of ceftriaxone above single dose values. Accumulation was more with the IM doses. Ceftriaxone concentrations in urine are high, as shown in Table 2.

Table 2. Average urinary concentrations (mcg/mL) of ceftriaxone after a single dose administration.

Dose	Route	Time after dose (hours)				
		0-2	2-4	4-8	8-12	12-24
0.5g	IV	526	366	142	87	70
0.5g	IM	115	425	308	127	96
1.0g	IV	995	855	293	147	132
1.0g	IM	504	628	418	237	ND
2.0g	IV	2,692	1,976	757	274	198

ND = not determined.

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

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

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

Table 3. Pharmacokinetic parameters of ceftriaxone in paediatric patients.

Parameter after 50mg/kg IV dose	Average value
Maximum plasma concentrations	216microgram/mL
Elimination half-life	4.6 hours
Plasma clearance	49mL/hour/kg
Volume of distribution	338mL/kg
CSF concentration in purulent meningitis	5.6microgram/mL
Range	1.3-18.5microgram/mL
Time after dose	3.7(±1.6) hours

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

Ceftriaxone crosses the placenta and appears in the milk in low concentrations. Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2g/day. However, in some patients with severely impaired renal function, the $t_{1/2}$ of ceftriaxone may be prolonged (37 to 52 hours) and dosage adjustment should be considered. Peak serum levels should be held below 280microgram/mL. Ceftriaxone was not removed to any significant extent from the plasma by haemodialysis. Plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

Table 4. Average pharmacokinetic parameters of ceftriaxone in humans.

Subject group	Elimination half-life (hours)	Plasma clearance (L/hour)	Volume of distribution (L)
Healthy subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly subjects (mean age 70.5 years)	8.9	0.83	10.7
Patients with renal impairment			
Haemodialysis (0.5mL/minute)*	14.7	0.65	13.7
Severe (5-15mL/minute)*	15.7	0.56	12.5
Moderate (16-30mL/minute)*	11.4	0.72	11.8
Mild (31-60mL/minute)*	12.4	0.70	13.3
Patients with liver disease	8.8	1.10	13.6

* Creatinine clearance

INDICATIONS

Treatment of the following infections when caused by susceptible aerobic organisms.

Lower respiratory tract infections. Caused by *Strep. pneumoniae*, Streptococcus sp. (excluding Enterococci), methicillin sensitive *Staph. aureus*, *H. influenzae*, *H. parainfluenzae*, Klebsiella sp. (including *K. pneumoniae*), *E. coli*, *E. aerogenes*, *P. mirabilis* and *Serratia marcescens*.

Skin and skin structure infections. Caused by methicillin sensitive *Staph. aureus*, methicillin sensitive *Staph. epidermidis*, Streptococcus group B, Streptococcus group G, *Strep. pyogenes*, *Strep. viridans*, Streptococcus sp. (excluding Enterococci), Peptostreptococcus sp., *E. coli*, *E. cloacae*, Klebsiella sp. (including *K. pneumoniae* and *K. oxytoca*), *P. mirabilis*, *M. morgani* and *S. marcescens*.

Urinary tract infections (complicated and uncomplicated). Caused by *E. coli*, *P. mirabilis*, *P. vulgaris*, *M. morgani* and Klebsiella sp. (including *K. pneumoniae*).

Uncomplicated gonorrhoea (cervical/ urethral and rectal). Caused by *N. gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

Bacterial septicaemia. Caused by *Strep. pneumoniae*, *E. coli* and *H. influenzae*.

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Bone infections. Caused by methicillin sensitive *Staph. aureus*, methicillin sensitive *Staph. epidermidis*, Streptococcus group B, *Strep. pneumoniae*, Streptococcus sp. (excluding Enterococci), *E.coli*, Enterobacter sp., *P. mirabilis* and *K. pneumoniae*.

Joint infections. Caused by methicillin sensitive *Staph. aureus*, *Strep. pneumoniae*, Streptococcus sp. (excluding Enterococci), *E. coli*, *P. mirabilis*, *K. pneumoniae* and Enterobacter sp.

Meningitis. The initial treatment, as a single agent, of meningitis in children and immunocompetent adults when presumed or proven to be caused by *H. influenzae* type b, *N. meningitidis*, *Strep. pneumoniae* or Enterobacteriaceae pending culture and sensitivity results.

Surgical prophylaxis. The preoperative administration of a single 1g dose of ceftriaxone may reduce the incidence of postoperative infections in patients undergoing vaginal or abdominal hysterectomy or cholecystectomy in high risk patients, surgical procedures which are classified as contaminated or potentially contaminated, and patients undergoing coronary artery bypass surgery. Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo controlled trials have been conducted.

Susceptibility testing. Before instituting treatment with ceftriaxone, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS

Ceftriaxone is contraindicated in patients with known hypersensitivity to beta-lactam antibiotics.

In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.

Hyperbilirubinaemic neonates, especially prematures, should not be treated with ceftriaxone. *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.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in newborns have been described. . 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 (see Post-marketing experience).

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Ceftriaxone is contraindicated in:

- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term newborns (up to 28 days of age)
 - with jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired
 - if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium (see Precautions, Adverse Effects and Interactions with other medicines).

Lignocaine should not be used as a diluent for intramuscular injection in patients who are hypersensitive to lignocaine.

PRECAUTIONS

Hypersensitivity to cephalosporins, penicillins or other drugs..

BEFORE THERAPY WITH CEFTRIAZONE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. ANAPHYLACTIC REACTIONS WITH FATAL OUTCOME HAVE BEEN REPORTED, EVEN IF A PATIENT IS NOT KNOWN TO BE ALLERGIC OR PREVIOUSLY EXPOSED TO ROCEPHIN OR OTHER CEPHALSOPORINS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS ADRENALINE AND OTHER EMERGENCY MEASURES. IF AN ALLERGIC REACTION OCCURS CEFTRIAZONE SHOULD BE DISCONTINUED.

Calcium containing solutions. In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing products. 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. 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. (See Contraindications, Adverse Effects, Pharmacokinetic properties and Interactions with other medicines.)

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Antibiotic associated pseudomembranous colitis..

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea 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. Hypertoxin producing 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.

Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used. Other causes of colitis should also be considered.

Immune mediated Haemolytic Anaemia

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

History of gastrointestinal disease. Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

Overgrowth of other non-susceptible organisms. Prolonged use of ceftriaxone may result in overgrowth of non-susceptible organisms (candida, fungi or other resistant microorganisms). Pseudomembraneous colitis is a rare undesirable effect caused by infection with *Clostridium difficile* during treatment with ceftriaxone. Therefore, the possibility of the disease should be considered in patients who present with diarrhea following antibacterial agent use. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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

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Gall bladder and kidney concretions/ precipitates. Ceftriaxone may precipitate in the gallbladder and kidneys and then be detectable as shadows on ultrasound. This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided – except for meningitis – because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended. (see ADVERSE REACTIONS). Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician.

Renal impairment and toxicity. Ceftriaxone has shown some evidence of renal toxicity in animals. Clinical studies have shown only transient elevations of serum urea and serum creatinine at the recommended dosages. Ceftriaxone is excreted via both biliary and renal excretion (see PHARMACOKINETICS). The half-life of ceftriaxone may be prolonged in some patients with renal failure; adjustment in dosage may be required. Concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly. Dosage adjustments should not be necessary in patients with hepatic dysfunction. In patients with both hepatic dysfunction and significant renal disease, ceftriaxone dosage requires close monitoring of serum concentrations.

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 (10mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

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

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis. Carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

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

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

Use in pregnancy (Category B1)

Category B1: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.*

Teratogenic effects. Reproductive studies (segment II) have been performed in mice and rats at doses up to 586mg/kg/day and no evidence of embryotoxicity, foetotoxicity or

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teratogenicity was seen. In primates at doses up to 84mg/kg/day, no embryotoxicity or teratogenicity was demonstrated. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

Use in lactation

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

Use in children

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described in Dosage and Administration. *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.

Because of the risk of precipitation of ceftriaxone-calcium (see Interactions with other medicines) Ceftriaxone is contraindicated in neonates requiring (or expected to require) treatment with calcium-containing I.V. solutions (including continuous calcium-containing infusions such as parenteral nutrition) (see CONTRAINDICATIONS).

Interactions with other medicines

No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide). Healthy adults treated with 3 mg ceftriaxone and 3mg/kg per day of tobramycin for three days did not show any enzymatic evidence of impaired renal function. 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 which has been associated with significant impairment of vitamin K dependent coagulation by some other cephalosporins and possible ethanol intolerance and bleeding problems of certain other cephalosporins.

Probenecid does not cause clinically significant changes in the elimination of ceftriaxone. Concomitant use does not confer a therapeutic benefit. In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone

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

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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.

Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives.

Consequently, it is advisable to use supplementary (non- hormonal) contraceptive measures during treatment and in the month following treatment.

Effects on Laboratory tests

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

Likewise, 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.

Haematological changes such as eosinophilia, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia. 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. During prolonged treatment the complete blood count should be done at regular intervals.

Effect on Ability to Drive or Operate Machinery

Since Ceftriaxone sometimes induces dizziness, the ability to drive and use machines can be impaired.

ADVERSE EFFECTS

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

Local reactions. Infrequent pain, induration or tenderness at the site of injection. Less frequently reported was phlebitis after intravenous administration. These may be minimised by slow (2-4 minutes) injection. Local reactions were increased if water was used as the diluent instead of lignocaine.

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

Haematological. Occasional eosinophilia, thrombocytosis and leucopenia. Less frequently reported were haemolytic anaemia, neutropenia, lymphopenia, granulocytopenia, thrombocytopenia and prolongation of the prothrombin time and bleeding. In very rare

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cases agranulocytosis has been reported (most of them after 10 days of treatment and following total doses of 20g or more).

Gastrointestinal. Occasional diarrhoea. Less frequently reported were nausea or vomiting, stomatitis, glossitis and dysgeusia. Incidence of diarrhoea was higher in women and children. Pseudomembranous colitis has been reported rarely.

Hepatic. Occasional elevations of ALT or AST. Less frequently reported were elevations of alkaline phosphatase and bilirubin. Symptomatic precipitation of ceftriaxone calcium salt in the gall bladder.

Shadows which have been mistaken for gallstones have been detected on sonograms of the gall bladder, 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.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

This disorder is rare in adults. In symptomatic cases, conservative nonsurgical management is recommended. Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the clinician.

Renal. Infrequent elevations of the serum urea. Less frequently reported were elevations of creatinine and the presence of casts in the urine. Crystalluria and oliguria have been reported very rarely. Renal adverse effects were somewhat more frequent in the elderly. 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.). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of ceftriaxone. There have been isolated reports of pancreatitis.

Central nervous system. Headache or dizziness were reported occasionally.

Genitourinary. Candidiasis or vaginitis were reported occasionally.

Miscellaneous. Diaphoresis, flushing and fever were reported occasionally. Other rarely observed adverse reactions include vertigo, leucocytosis, lymphocytosis, monocytosis, basophilia, jaundice, glycosuria, haematuria, anaphylactic or anaphylactoid reactions eg. bronchospasms, oedema, shivering, serum sickness, abdominal pain, flatulence, dyspepsia, palpitations, epistaxis and superinfections with non-susceptible micro-organisms. Isolated cases of severe cutaneous reactions (Stevens-Johnson syndrome or Lyell's syndrome/ toxic epidermal necrolysis) have been reported.

Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions or products, even via different infusion lines

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem.

The high risk of precipitation in newborns is due to their low blood volume and the longer half life of ceftriaxone compared with adults (see Contraindications, Precautions and Pharmacokinetic properties).

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. (see Contraindications).

Post-marketing experience

In addition to the adverse reactions reported during clinical trials, the following adverse experiences have been reported during clinical practice in patients treated with ceftriaxone. Data are generally insufficient to allow an estimate of incidence or to establish causation.

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.

Gastrointestinal:

Stomatitis and glossitis.

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Genitourinary:

Oliguria.

Dermatologic:

Exanthema, allergic dermatitis, urticaria, edema. As with many medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

DOSAGE AND ADMINISTRATION

Ceftriaxone may be administered intravenously or intramuscularly.

The recommended adult daily dose is 1 to 2g 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.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250mg 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 1g administered 30 minutes to 2 hours before surgery is recommended.

For the treatment of serious miscellaneous infections in children, the recommended total daily dose is 50 to 75mg/kg (not to exceed 2g), given once per day or in divided doses every twelve 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 to 14 days. In special conditions (e.g. endocarditis, osteomyelitis, infected joints) 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.

Each gram of ceftriaxone contains 3.6x mmol sodium. To be taken into consideration in patients on a controlled diet.

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 280microgram/mL.

Ceftriaxone contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, store at 2-8°C for not more than 24 hours. The solutions are yellowish in colour; this characteristic of the active ingredient is of no significance to

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the efficacy or tolerance of the drug. A slight opalescence may be seen in the reconstituted solution.

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 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. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (See Contraindications, Precautions for use and Adverse Effects).

Ceftriaxone 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, fluconazole and aminoglycosides.

Intramuscular injection. Ceftriaxone 0.25 or 0.5g dissolved in 2mL, or ceftriaxone 1g in 3.5mL of lignocaine 1% solution, administered by deep intragluteal injection. It is recommended that no more than 1g be injected on either side. The lignocaine solution must never be administered intravenously. In case lignocaine is used as a solvent, ceftriaxone solutions should only be used for intramuscular injection. Ceftriaxone should be injected well into the body of a relatively large muscle mass. Intramuscular injection of ceftriaxone without lignocaine solution is painful.

Intravenous injection. Ceftriaxone 0.25 or 0.5g dissolved in 5mL, or ceftriaxone 1g in 10mL of water for injections, administered by direct intravenous injection lasting two to four minutes.

Intravenous infusion. Ceftriaxone 2g dissolved in approximately 40mL of one of the following infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% and glucose 2.5%, glucose 5%, glucose 10%. The infusion should be given over a period of at least 30 minutes.

OVERDOSAGE

Excessive serum concentrations of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. Treatment of overdosage should be symptomatic and consist of general supportive measures. In the case of overdose nausea, vomiting, diarrhoea, can occur. There is no specific antidote. Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Vials (rubber stoppered); 1g, 2g: 1, 5 or 10 vials per pack

Not all presentations may be marketed in Australia.

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Storage

Powder for injection

Store below 25°C. Protect from light and moisture.

Reconstituted solution

Store at 2-8°C (Refrigerate. Do not freeze) for not more than 24 hours.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd

ABN 60 075 449 553

54 Waterloo Road

Macquarie Park, NSW 2113

Australia

Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of First inclusion on the Australian Register of Therapeutic Goods (The ARTG):

25 July 2003

Date of most recent amendment: 14 June 2016