

ROCEPHIN[®]

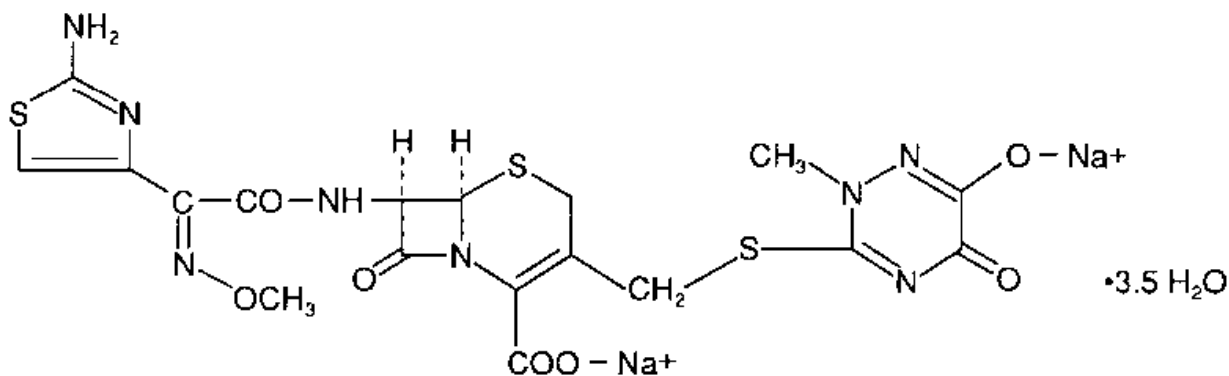
ceftriaxone sodium

(CAS registry number: 104376-79-6)

DESCRIPTION

ROCEPHIN (ceftriaxone sodium) is a sterile, semisynthetic, broad spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is sodium (Z)-(6*R*,7*R*)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-(methoxy-imino)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, hydrate (2:7).

The chemical formula of ceftriaxone sodium is C₁₈H₁₆N₈Na₂O₇S₃ · 3.5H₂O. It has a calculated molecular weight of 661.59 and the following structural formula:



Ceftriaxone sodium is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 5% aqueous solution is approximately 6-8. The colour of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

ROCEPHIN contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

PHARMACOLOGY

Pharmacokinetics

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

Table 1: Average Ceftriaxone Plasma Concentrations After Single Dose Administration

Dose/ Route	Average Plasma Concentrations (mcg/mL) (Time from End of Administration)								
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	16 hr	24 hr
0.5 g i.v.	82	59	48	37	29	23	15	10	5
0.5 g i.m.	30	41	43	39	31	25	16	ND	ND
1 g i.v.	151	111	88	67	53	43	28	18	9
1 g i.m.	40	68	76	68	56	44	29	ND	ND
2 g i.v.	257	192	154	117	89	74	46	31	15

I.V. doses were infused at a constant rate over 30 minutes.

I.M. doses were administered with lignocaine.

ND = Not determined.

Mean maximum plasma concentrations following I.M. injection occurred between two and three hours post-dosing. Multiple I.V. or I.M. doses ranging from 0.5 to 2 g at 12 to 24 hour intervals resulted in 15 to 36% accumulation of ceftriaxone above single dose values. Accumulation was more with the I.M. doses.

Ceftriaxone concentrations in urine are high, as shown in Table 2.

Table 2: Urinary Concentrations (mcg/mL) of Ceftriaxone After Single Dose Administration

Dose/Route	Average Urinary Concentrations (mcg/mL)				
	0-2 hr	2-4 hr	4-8 hr	8-12 hr	12-24 hr
0.5 g i.v.	526	366	142	87	70
0.5 g i.m.	115	425	308	127	96
1 g i.v.	995	855	293	147	132
1 g i.m.	504	628	418	237	ND*
2 g i.v.	2692	1976	757	274	198

*ND = Not determined.

Thirty-three 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 1 g I.V. dose, average concentrations of ceftriaxone, determined from one to three hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/g in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma. There were, however, wide individual variations in levels.

Over a 0.15 to 3 g 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 13.5 L; plasma clearance from 0.58 to 1.45 L/hr and renal clearance from 0.32 to 0.73 L/hr. Ceftriaxone is reversibly bound to

human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of 25 mcg/mL to a value of 85% bound at 300 mcg/mL. Protein binding is reduced in children and in uremic patients. The *in vitro* activity of ceftriaxone is decreased 2 to 8 fold by the presence of human serum.

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

Table 3: Average Pharmacokinetic Parameters of Ceftriaxone in Paediatric Patients

	50 mg/kg i.v.
Maximum plasma concentrations (mcg/mL)	216
Elimination half-life (hr)	4.6
Plasma clearance (mL/hr/kg)	49
Volume of distribution (mL/kg)	338
CSF concentrations – in purulent meningitis (mcg/mL)	5.6
Range (mcg/mL)	1.3 - 18.5
Time after dose (hr)	3.7 (±1.6)

The half life of ceftriaxone in neonates ranges from 7.2 - 19 hours and in infants over six weeks of age from 4.0-6.6 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 doses up to 2 g/day. However in some patients with severely impaired renal function the $t_{1/2}$ of ceftriaxone may be prolonged (37 - 52 hours) and dosage adjustment should be considered. Peak serum levels should be held below 280 mcg/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 (hr)	Plasma Clearance (L/hr)	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 patients (0.5 mL/min)*	14.7	0.65	13.7
Severe (5-15 mL/min)	15.7	0.56	12.5
Moderate (16-30 mL/min)	11.4	0.72	11.8
Mild (31-60 mL/min)	12.4	0.70	13.3
Patients with liver disease	8.8	1.1	13.6

* Creatinine clearance.

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 & 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* species (including *K. pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii* and *Serratia marcescens*.

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

GRAM-POSITIVE AEROBES: *Staphylococcus aureus* (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note: methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta-haemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae*, Group G streptococci, *Streptococcus viridans* and *Streptococcus* species (Note: Most species of Group D streptococci including *Streptococcus faecalis* and *Streptococcus faecium* are resistant).

SUSCEPTIBILITY TESTING: Standard susceptibility disk method. Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, Am J Clin Pathol 45:493-496, 1966; Standardized Disk Susceptibility Test, Federal Register 39: 19182-19184, 1974; National Committee for Clinical Laboratory Standards Approved Standard: ASM-2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to

ceftriaxone. Laboratory results of the standardized single-disk susceptibility test using a 30 mcg ceftriaxone disk should be interpreted according to the following three criteria:

1. Susceptible organisms produce zones of 21 mm or greater, indicating that the tested organism is likely to respond to therapy.
2. Organisms that produce zones of 14 to 20 mm 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 zones of 13 mm or less, indicating that other therapy should be selected.

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

Standardized procedures require use of control organisms. The 30 mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853, respectively.

DILUTION TECHNIQUES: A bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 8 mcg/mL. Organisms are considered resistant to ceftriaxone if the MIC is greater than 32 mcg/mL. Organisms having a MIC value of equal to or less than 32 mcg/mL, but greater than 8 mcg/mL, are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg urine), in which high antibiotic levels are attained. *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. 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 0.5 mcg/mL. The range for the *S. aureus* strain should be 1 to 2 mcg/mL.

INDICATIONS

ROCEPHIN is indicated for the treatment of the following infections when caused by susceptible aerobic organisms.

LOWER RESPIRATORY TRACT INFECTIONS caused by *S. pneumoniae*, Streptococcus species (excluding enterococci), methicillin sensitive *S. aureus*, *H. influenzae*, *H. parainfluenzae*, Klebsiella species (including *K. pneumoniae*), *E. coli*, *E. aerogenes*, *Proteus mirabilis* and *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by methicillin sensitive *S. aureus*, methicillin sensitive *S. epidermidis*, Streptococcus Group B, Streptococcus Group G, *Streptococcus pyogenes*, *Streptococcus viridans*, Streptococcus species (excluding enterococci), Peptostreptococcus species, *E. coli*, *E. cloacae*, Klebsiella species (including *K. pneumoniae*, *K. oxytoca*), *Proteus mirabilis*, *Morganella morganii*, *Serratia marcescens*.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli*, *Proteus mirabilis*, *Proteus vulgaris*, *M. morganii* and Klebsiella species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHOEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoea*, including both penicillinase and non penicillinase producing strains.

BACTERIAL SEPTICEMIA caused by *S. pneumoniae*, *E. coli* and *H. influenzae*.

BONE INFECTIONS caused by methicillin sensitive *S. aureus*, methicillin sensitive *S. epidermidis*, Streptococcus Group B, *S. pneumoniae*, Streptococcus species (excluding enterococci), *E. coli*, Enterobacter species, *P. mirabilis* and *K. pneumoniae*.

JOINT INFECTIONS caused by methicillin sensitive *S. aureus*, *S. pneumoniae*, Streptococcus species (excluding enterococci), *E. coli*, *P. mirabilis*, *K. pneumoniae* and Enterobacter species.

MENINGITIS: The initial treatment, as a single agent, of meningitis in children and immunocompetent adults when presumed or proven to be caused by *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Streptococcus pneumoniae* or Enterobacteriaceae pending culture and sensitivity results.

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 g dose of ceftriaxone may reduce the incidence of post-operative 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 allergy to the cephalosporin class of antibiotics or a major allergy to penicillin (anaphylaxis, angioneurotic oedema, urticaria).

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

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.

Because of the risk of precipitation of ceftriaxone-calcium, ROCEPHIN 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 Interactions with other medicines and Use in Children).

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 ROCEPHIN and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both

ROCEPHIN 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 ROCEPHIN 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).

PRECAUTIONS

Hypersensitivity to Cephalosporins, Penicillins or other medicines

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 CEPHALOSPORINS. 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 ceftriazone and calcium-containing solutions or any other calcium-containing products. However, ceftriazone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines (see CONTRAINDICATIONS, Interactions with other medicines and ADVERSE EFFECTS, Post-marketing experience).

***Clostridium difficile* associated diarrhoea**

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including ROCEPHIN, 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 diarrhoea 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 which delay peristalsis e.g. opiates and diphenoxylate with atropine (LOMOTIL) may prolong and/or worsen the condition and should not be used.

Other causes of colitis should also be considered.

History of Gastrointestinal Disease

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

Immune mediated Haemolytic Anaemia

Immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ROCEPHIN. 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.

Overgrowth of Other Non-Susceptible Organisms

Prolonged use of ROCEPHIN may result in overgrowth of non-susceptible organisms. 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 rarely reported in patients treated with ROCEPHIN. Most patients presented with risk factors for biliary stasis and biliary sludge, eg preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of ROCEPHIN-related biliary precipitation can therefore not be ruled out.

Gall Bladder Concretions/Precipitates

Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder, usually following doses higher than the standard recommended dose. These shadows are, however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ROCEPHIN therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended.

Discontinuation of ROCEPHIN 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, ROCEPHIN dosage requires close monitoring of serum concentrations.

Alterations in Clotting Time

Alterations in prothrombin times have occurred rarely in patients treated with ROCEPHIN. Patients with impaired vitamin K synthesis or low vitamin K stores (eg chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during ROCEPHIN treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Use of Lignocaine Hydrochloride in Patients with Impaired Liver Function

Repeated use of lignocaine hydrochloride should be avoided in patients with severe liver 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 586 mg/kg/day.

Use in Pregnancy – Category B1

Teratogenic Effects: Reproductive studies (Segment II) have been performed in mice and rats at doses up to 586 mg/kg/day and no evidence of embryotoxicity, foetotoxicity or teratogenicity was seen. In primates, at doses up to 84 mg/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 medicine should be used during pregnancy only if clearly needed.

Non-Teratogenic 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 586 mg/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 nursing woman.

Use in Children

Safety and effectiveness of ceftriaxone in 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 given to neonates who may be at risk of developing bilirubin encephalopathy (especially premature infants) (see CONTRAINDICATIONS).

Because of the risk of precipitation of ceftriaxone-calcium (see Interactions with other medicines) ROCEPHIN 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

Ceftriaxone does not contain an N-methylthiotetrazole moiety which has been associated with significant impairment of Vitamin-K dependent coagulation by some 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 ROCEPHIN vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ROCEPHIN is mixed with calcium-containing solutions in the same I.V. administration line. ROCEPHIN must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ROCEPHIN 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 DOSAGE AND ADMINISTRATION and CONTRAINDICATIONS).

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

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

Laboratory Tests

In patients treated with ceftriaxone the Coombs' test may become false-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 ($< 500/\text{mm}^3$) 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.

ADVERSE EFFECTS

Ceftriaxone is generally well tolerated. In clinical trials, the following adverse effects, 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 I.V. administration. 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, allergic dermatitis.

HAEMATOLOGICAL - occasional eosinophilia, thrombocytosis and leukopenia. Less frequently reported were haemolytic anaemia, neutropenia, lymphopenia, granulocytopenia, thrombocytopenia and prolongation of the prothrombin time and bleeding. In very rare cases agranulocytosis has been reported.

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 SGOT or SGPT. Less frequently reported were elevations of alkaline phosphatase, bilirubin. Symptomatic precipitation of ceftriaxone calcium salt in the gall bladder.

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.

CENTRAL NERVOUS SYSTEM - headache or dizziness were reported occasionally.

GENITOURINARY - moniliasis or vaginitis were reported occasionally.

MISCELLANEOUS – diaphoresis, flushing and fever were reported occasionally.

Other rarely observed adverse reactions include leukocytosis, lymphocytosis, monocytosis, basophilia, jaundice, glycosuria, haematuria, bronchospasm, oedema, shivering, serum sickness, abdominal pain, flatulence, dyspepsia, palpitations and epistaxis.

Isolated cases of severe cutaneous reactions (Stevens Johnson syndrome or Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Post-marketing experience

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys 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.

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).

DOSAGE AND ADMINISTRATION

Dosage

ROCEPHIN 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.

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 eg

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 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 medicine. A slight opalescence may be seen in the reconstituted solution.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ROCEPHIN vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ROCEPHIN is mixed with calcium-containing solutions in the same I.V. administration line. ROCEPHIN must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ROCEPHIN and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see CONTRAINDICATIONS and Use in Children).

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (I.V. or oral).

ROCEPHIN should also not be mixed with or piggybacked into solutions containing other antimicrobial medicines 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: ROCEPHIN 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. ROCEPHIN should be injected well into the body of a relatively large muscle mass. Intramuscular injection of ROCEPHIN *without* lignocaine solution is painful.

Intravenous injection: ROCEPHIN 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 ROCEPHIN 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%

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.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

For intramuscular or intravenous injection:

Vials containing powder equivalent to 1 g ceftriaxone.

Packs of 1 and 10

For intravenous infusion:

Vials containing powder equivalent to 2 g ceftriaxone.

Packs of 1.

Store below 30°C.

ROCEPHIN is sensitive to light. Keep the vial in the outer carton in order to protect from light.

Shelf life (unreconstituted vials): 3 years.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Disposal of Syringes and Sharps

The following points should be followed:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Avoid placing the used sharps container in household waste.

STABILITY

Reconstituted solutions of ROCEPHIN are stable for six hours at room temperature (25 °C) and for twenty-four hours if stored under refrigeration (5 °C).

SPONSOR

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