SUMMARY OF PRODUCT CHARACTERISTICS

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Rocephin is a long acting, broad spectrum cephalosporin antibiotic for parenteral use

1.2 Type of Dosage Form

Powder for solution for injection

Powder for solution for infusion

1.3 Route of Administration

- intramuscular injection
- intravenous injection
- intravenous infusion

1.4 Sterile / Radioactive Statement

Not applicable

1.5 Qualitative and Quantitative Composition

Active ingredient: ceftriaxone in the form of the disodium salt.
Vials containing dry substance equivalent to 0.25 g, 0.5 g, 1 g or 2 g ceftriaxone.

Solvent for parenteral use: The solvent ampoule for i.v. injection contains sterile water for injections and for i.m. injection contains 1% lidocaine hydrochloride solution. 1 ml solvent for i.m. injection contains 10.66 mg lidocaine hydrochloride monohydrate equivalent to 10 mg anhydrous lidocaine hydrochloride.

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

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Infections caused by pathogens sensitive to Rocephin, e.g.:

– sepsis; [1,2,3,4]

– meningitis; [5,6,7]

– disseminated Lyme borreliosis (early and late stages of the disease); [8,9,10,11]

– abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);[12,13,14,15]

– infections of the bones, joints, soft tissue, skin and of wounds; [16,17,18]

– infections in patients with impaired defense mechanisms; [19,20,21,22]

– renal and urinary tract infections; [23,24,25]

– respiratory tract infections, particularly pneumonia, and ear, nose and throat infections; [26,27,2829]

– genital infections, including gonorrhoea. [30,31,32,33]

And perioperative prophylaxis of infections. [34,35,36]

2.2 Dosage and Administration

Standard dosage
Adults and children over 12 years

The usual dosage is 1-2 g of Rocephin *once daily* (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.[37]

Duration of therapy

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Rocephin should be continued for a minimum of 48-72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination therapy

Synergy between Rocephin and aminoglycosides has been demonstrated with many gram-negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life threatening infections due to microorganisms such as *Pseudomonas aeruginosa*. Due to chemical

incompatibility between Rocephin and aminoglycosides, the two drugs must be administered separately at the recommended dosages [38, 39].
Chemical incompatibility with Rocephin has also been observed with IV administration of amsacrine, vancomycin and fluconazole. [89, 90, 91, 163, 164, 165, 166]

Method of administration
As a general rule the solutions should be used immediately after preparation.

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 - 8°C). The solutions range in color from pale yellow to amber, depending on the concentration and length of storage. The coloration of the solutions is of no significance for the efficacy or tolerance of the drug. [40, 41]

Intramuscular injection. For i.m. injection, Rocephin 250 mg or 500 mg is dissolved in 2 ml, and Rocephin 1 g in 3.5 ml, of 1% lidocaine hydrochloride solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site.

The lidocaine solution should never be administered intravenously (*see section 2.3 Contraindications*). [42]

Intravenous injection. For i.v. injection, Rocephin 250 mg or 500 mg is dissolved in 5 ml, and Rocephin 1 g in 10 ml, sterile water for injections. The intravenous administration should be given over 2-4 minutes. [43]

Intravenous infusion. The infusion should be given over at least 30 minutes. For i.v. infusion, 2 g Rocephin is dissolved in 40 ml of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxy ethyl starch 6-10%, water for injections. Rocephin 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. [44, 45, 46, 47]

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 IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Rocephin is mixed with calcium-containing solutions in the same IV administration line. Rocephin must not be

administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, 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 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction*). [151,154, 155]

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral). [151,154,155]

2.2.1 Special Dosage Instructions

Patients with hepatic impairment

In patients with liver *damage*, there is no need for the dosage to be reduced provided renal function is not impaired. [48, 49]

Patients with renal impairment

In patients with impaired renal function, there is no need to reduce the dosage of Rocephin provided hepatic function is not impaired. [48,49] Only in cases of preterminal renal failure (creatinine clearance <10 ml/min) should the Rocephin dosage not exceed 2 g daily.
Ceftriaxone is not removed by peritoneal- or hemodialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis.

Patients with severe renal and hepatic impairment

In patients with both severe renal and hepatic dysfunction, clinical monitoring for safety and efficacy is advised.

Elderly

The dosages recommended for adults require no modification in elderly patients, provided there is no severe renal and hepatic impairment. [53]

Children

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for once daily administration:
Neonates (up to 14 days): 20-50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. [54, 55]
Rocephin is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) (*see section 2.3 contraindications*).

Rocephin is contraindicated in neonates (≤28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (*see 2.3 Contraindications*). [153,154,155]

For neonates, infants, and children (15 days to 12 years): 20-80 mg/kg once daily.

For children with bodyweights of 50 kg or more, the usual adult dosage should be used.
Intravenous doses of ≥ 50 mg/kg bodyweight, in infants and children up to 12 years of age, should be given by infusion over at least 30 minutes.[1, 2, 55] In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy [167].

Meningitis
In bacterial meningitis in *infants and children*, treatment begins with doses of 100 mg/kg (up to a maximum of 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. The following duration of therapy has shown to be effective:

Neisseria meningitidis	4 days
Haemophilus influenzae	6 days
Streptococcus pneumoniae	7 days [5,56]

Lyme borreliosis
50 mg/kg to a maximum of 2 g in children and adults, once daily for 14 days.[57,58]

Gonorrhoea (penicillinase-producing and nonpenicillinase-producing strains)
A single i.m. dose of 250 mg.[30,33]

Perioperative prophylaxis

A single dose of 1-2 g depending on the risk of infection of 30-90 minutes prior to surgery.[59] In colorectal surgery, administration of Rocephin with or without a 5-nitroimidazole, e.g. ornidazole (separate administration, *see 2.2 Dosage and Administration*) has been proven effective.[60,61,62,63]

2.3 Contraindications

Hypersensitivity

Rocephin is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam agents may be at greater risk of hypersensitivity to ceftriaxone (*see section 2.4.1 Warnings and Precautions General – Hypersensitivity*).

Lidocaine

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent (*see section 2.2 Dosage and Administration*). See contraindications section in the prescribing information of lidocaine. Ceftriaxone solutions containing lidocaine should never be administered intravenously [42].

Premature Neonates

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

Hyperbilirubinemic newborns

Hyperbilirubinemic 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.

Neonates and Calcium Containing IV Solutions

Rocephin is contraindicated in neonates (≤28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (*see 2.2 Dosage and Administration and 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction*). [153,154,155]

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 2.6.2 Post Marketing*). [148,154,155]

2.4 Warnings and Precautions

2.4.1 General

Hypersensitivity

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (*see section 2.6.2 Post Marketing*). In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of hypersensitivity reactions to ceftriaxone, to other cephalosporins, or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of hypersensitivity to other beta-lactam agents. [162, 183, 196, 197]

Hemolytic Anemia

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including Rocephin. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and ceftriaxone discontinued until the etiology is determined. [156]

Clostridium difficile associated diarrhea (CDAD)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Rocephin, 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. [157,158,159,160,161]

C. difficile produces toxins A and B which contribute to the development of CDAD. Toxin hyperproducing strains of C. difficile cause increased morbidity and mortality, as these infections

can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. [157,158,159,160,161]

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. [157,158,159,160,161]

Superinfections

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents. [67,68,69,70]

Calcium-ceftriaxone precipitates

Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving ceftriaxone, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in pediatric patients. Precipitates disappear after discontinuation of ceftriaxone therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of ceftriaxone treatment should be considered by the physician based on an individual benefit-risk assessment. [71, 168, 169, 170, 171, 172]

In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. However, ceftriaxone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines (*see 2.3 Contraindications for information regarding newborns, 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction, and 2.6.2 Post Marketing*).

Pancreatitis

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, e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of Rocephin- related biliary precipitation cannot be ruled out. [72]

Pediatrics

Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described under Dosage and administration.[73,74,75] Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Rocephin should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy (*see 2.3 Contraindications*). [76,77,78]

Blood Monitoring

During prolonged treatment the complete blood count should be done at regular intervals. [70,79]

2.4.2 Drug Abuse and Dependence

Not applicable

2.4.3 Ability to Drive and Use Machines

During treatment with Rocephin, undesirable effects may occur (e.g. dizziness), which may influence, the ability to drive and use machines (*see section 2.6 Undesirable Effects*). Patients should be cautious when driving or operating machinery.

2.4.4 Laboratory Tests

Influence on diagnostic tests

In patients treated with Rocephin the Coombs' test may become falsely positive.[103] Rocephin, like other antibiotics, may result in false-positive test results for galactosemia.[104]

Likewise, nonenzymatic methods for the glucose determination in urine may give false-positive results. [105] For this reason, urine-glucose determination during therapy with Rocephin should be done enzymatically. [106]

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary. [198, 199, 200]

2.4.5 Interactions with other Medicinal Products and other Forms of Interaction

No impairment of renal function has so far been observed after concurrent administration of large doses of Rocephin and potent diuretics (e.g. furosemide). [80] There is conflicting evidence

regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels and renal function in clinical practice should be closely adhered to in such cases. [81,184,185,186,187] No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of Rocephin.[82] Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.[83,84] The elimination of Rocephin is not altered by probenecid. [85,86,87]

In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. [88]

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 IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Rocephin is mixed with calcium-containing solutions in the same IV administration line. Rocephin must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, 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-calicum (see 2.2 Dosage and Administration and 2.3 Contraindications). [151,154,155]

Concomitant use of ceftriaxone with Vitamin K antagonists may increase the risk of bleeding [173, 174, 175]. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone (*see section 2.6 Undesirable Effects*).

2.5 Use in Special Populations

2.5.1 Pregnancy

Ceftriaxone crosses the placental barrier.[92] Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed. [93,94,95,96,97,98]

2.5.2 Labor and Delivery

No text

2.5.3 Nursing Mothers

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman. [92,99]

2.5.4 Pediatric Use

Refer to special dosage instructions

2.5.5 Geriatric Use

Refer to special dosage instructions

2.5.6 Renal Impairment

Refer to special dosage instructions

2.5.7 Hepatic Impairment

Refer to special dosage instructions

2.6 Undesirable Effects [100,101,102, 176, 201]

2.6.1 Clinical Trials

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

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

The following convention has been used for the classification of frequency:

Very common (≥ 1/10)

Common (≥ 1/100 - < 1/10)

Uncommon (≥ 1/1000 - < 1/100)

Rare (≥ 1/10000 - < 1/1000)

Table 1 Tabulated List of Adverse Reactions

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

2.6.1.1 Laboratory Abnormalities

No text

2.6.2 Post Marketing

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

Systemic side effects

Gastrointestinal complaints: pancreatitis, stomatitis and glossitis.

Hematological changes: Isolated cases of agranulocytosis (< 500/mm^3) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Skin reactions: acute generalized exanthematous pustulosis (AGEP) [177] and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson syndrome or Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Nervous system disorders: convulsion [168, 178, 179]

Infections and Infestations: superinfection

Other, rare side effects: symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

Interaction with calcium

Two in vitro studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation. [153,154,155]

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 interavenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (*see 2.4.1 Warnings and Precautions, General*). [148,154,155]

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

Local side effects

In rare cases, phlebitis reactions occurred after i.v. administration.[68,70] These may be minimized by slow (2-4 minutes) injection.

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

2.6.2.1 Laboratory Abnormalities

No data.

2.7 Overdose

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic. [107,108,109]

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS [110]

3.1 Pharmacodynamic Properties

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 ß-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 2.1 Therapeutic Indication(s)*):

Gram-positive aerobes

Staphylococcus aureus (methicillin-sensitive), Staphylococci coagulase-negative, *Streptococcus pyogenes* (ß-hemolytic, group A), *Streptococcus agalactiae* (ß-hemolytic, group B), ß-hemolytic Streptococci (non-group A or B), *Streptococcus viridans, Streptococcus pneumoniae.*

Note: Methicillin-resistant *Staphylococcus* spp. is resistant to cephalosporins, including ceftriaxone. In general, *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram-negative aerobes

Acinetobacter lwoffi, Acinetobacter anitratus (mostly *A. baumanii*)*, *Aeromonas hydrophila, Alcaligenes faecalis, Alcaligenes odorans*, *Alcaligenes*-like bacteria, *Borrelia burgdorferi, Capnocytophaga* spp., *Citrobacter diversus* (including *C. amalonaticus*), *Citrobacter freundii*, Escherichia coli, Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter* spp. (other)*, *Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae***, *Moraxella catarrhalis* (former *Branhamella catarrhalis*), *Moraxella osloensis, Moraxella* spp. (other), *Morganella morganii, Neisseria gonorrhoea, Neisseria meningitidis, Pasteurella multocida, Plesiomonas shigelloides, Proteus mirabilis, Proteus penneri*, Proteus vulgaris*, 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 ß-lactamase.

** Some isolates of these species are resistant due to production of extended spectrum, plasmid-mediated ß-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. With a few exceptions clinical *P. aeruginosa* isolates are resistant to ceftriaxone.

Anaerobic organisms

Bacteroides spp. (bile-sensitive)*, *Clostridium* spp. (excluding *C. difficile*), *Fusobacterium nucleatum, Fusobacterium* spp. (other), *Gaffkia anaerobica* (formerly *Peptococcus*), *Peptostreptococcus* spp.

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

Note: Many strains of ß-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
Dilution test inhibitory concentrations in mg/l	=8	16-32	=64
Diffusion test (disk with 30 µg ceftriaxone), inhibition zone diameter in mm	=21	20-14	=13

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.

3.1.1 Mechanism of Action

No text

3.1.2 Clinical / Efficacy Studies

No text

3.2 Pharmacokinetic Properties

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, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone. [48,111,112]

3.2.1 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.[113,114,115] 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.[115]

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively [182]. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. [183]

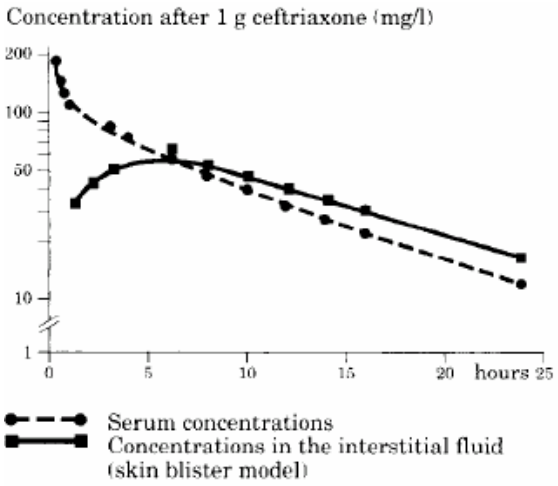
3.2.2 Distribution

The volume of distribution of ceftriaxone is 7-12 l.[111,116,117,118,119,120] 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.[121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138]

On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours (*see figure*). [139]

Protein binding

Ceftriaxone is reversibly bound to albumin.Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l) **[**185, 186, 187, 188**]**.



Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. [180, 181]

Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.[92]

3.2.3 Metabolism

Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.[111]

3.2.4 Elimination

Total plasma clearance is 10-22 ml/min.[111,112,116,117,118,119,120] Renal clearance is 5-12 ml/min.[111,112,116,117,118,120]

50-60% of ceftriaxone is excreted unchanged in the urine, while 40-50% is excreted unchanged in the bile.[48,85] The elimination half-life in adults is about 8 hours.[113]

3.2.5 Pharmacokinetics in Special Populations

Gender

No text

Race

No text

Patients with renal or hepatic impairment

In patients with *renal* [48, 49, 50, 107] *or hepatic dysfunction* [48, 49, 143], the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased, (less than two fold), even in patients with severely impaired renal function.

The modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance [189, 190, 191].

Elderly

In elderly persons aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Children

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults. [192, 193, 194, 195]

3.3 Preclinical Safety

3.3.1 Carcinogenicity

No text

3.3.2 Mutagenicity

No text

3.3.3 Impairment of Fertility

No text

3.3.4 Teratogenicity

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

3.3.5 Other

No text

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Do not store above 30°C, keep vial in the outer container.[149] Solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 - 8°C).

4.2 Special Instructions for Use, Handling and Disposal

This medicine should not be used after the expiry date (EXP) shown on the pack.

Packs: Described as per local requirements

Disposal of syringes/sharps

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- 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.

- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established ‘collection systems’ if available in your location.