SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone 1g Powder for Solution for Injection- Nirixone 1gm

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ceftriaxone sodium equivalent to 1g ceftriaxone per vial.

3. PHARMACEUTICAL FORM

1 g Powder for solution for injection or infusion

Powder for solution for injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone is indicated for the treatment of the following infections in adults and childrenincluding term neonates (from birth):

- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

Ceftriaxone may be used

For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults.

For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults andchildren including neonates from 15 days of age.

For pre-operative prophylaxis of surgical site infections.

In the management of neutropenic patients with fever that is suspected to be due to a bacterialinfection.

In the treatment of patients with bacteraemia that occurs in association with, or is suspected to beassociated with, any of the infections listed above.

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible rangeof causative bacteria would not fall within its spectrum.

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dose depends on the severity, susceptibility, site and type of infection and on the age and Hepato-renal function of the patient.

The doses recommended in the tables below are the generally recommended doses in theseindications. In particularly severe cases, doses at the higher end of the recommended range shouldbe considered.

Adults and children over 12 years of age (≥ 50 kg)

Ceftriaxone Dosage*	**Treatment frequency****	**Indications**
1 - 2 g	Once daily	Community acquired pneumonia
		Acute exacerbations of chronic obstructive pulmonary disease
		Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
2 g	Once daily	Hospital acquired pneumonia
		Complicated skin and soft tissue infections
		Infections of bones and joints
2 – 4 g	Once daily	Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
		Bacterial endocarditis
		Bacterial meningitis

*In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g dailyare administered.

Indications for adults and children over 12 years of age (≥ 50 kg) that require specific dosageschedules:

Acute otitis media

A single intramuscular dose of Ceftriaxone 1-2 g can be given. Limited data suggest that in caseswhere the patient is severely ill or previous therapy has failed, Ceftriaxone may be effective whengiven as an intramuscular dose of 1-2 g daily for 3 days.

Pre-operative prophylaxis of surgical site infections.

2 g as a single pre-operative dose.

Gonorrhea

500 mg as a single intramuscular dose.

Syphilis

The generally recommended doses are 500 mg -1 g once daily increased to 2 g once daily forneurosyphilis for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, arebased on limited data. National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

2 g once daily for 14-21 days. The recommended treatment durations vary and national or localguidelines should be taken into consideration.

Paediatric population

Neonates, infants and children 15 days to 12 years of age (< 50 kg)

For children with bodyweight of 50 kg or more, the usual adult dosage should be given.

Ceftriaxone Dosage*	**Treatment frequency****	**Indications**
50-80 mg/kg	Once daily	Intra-abdominal infections
		Complicated urinary tract infections (including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
50-100 mg/kg (Max 4 g)	Once daily	Complicated skin and soft tissue infections
		Infections of bones and joints
		Management of neutropenic patients with fever that is suspected to

		be due to a bacterial infection
80-100 mg/kg (max 4 g)	Once daily	Bacterial meningitis
100 mg/kg (max 4 g)	Once daily	Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should beconsidered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g dailyare administered.

Indications for neonates, infants and children 15 days to 12 years (< 50 kg) that require specificdosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg canbe given. Limited data suggest that in cases where the child is severely ill or initial therapy hasfailed, Ceftriaxone may be effective when given as an intramuscular dose of 50 mg/kg daily for 3days.

Pre-operative prophylaxis of surgical site infections

50 - 80 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended doses are 75-100 mg/kg (max 4 g) once daily for 10 - 14 days. Thedose recommendations in syphilis, including neurosyphilis, are based on very limited data.National or local guidance should be taken into consideration.

Disseminated Lyme borreliosis (early [Stage II] and late [Stage III])

50–80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and nationalor local guidelines should be taken into consideration.

Neonates 0-14 days

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

Ceftriaxone Dosage*	**Treatment frequency****	**Indications**
20-50 mg/kg	Once daily	Intra-abdominal infections
		Complicated skin and soft tissue infections
		Complicated urinary tract infections

		(including pyelonephritis)
		Community acquired pneumonia
		Hospital acquired pneumonia
		Infections of bones and joints
		Management of neutropenic patients with fever that is suspected to be due to a bacterial infection
50 mg/kg	Once daily	Bacterial meningitis
		Bacterial endocarditis

* In documented bacteraemia, the higher end of the recommended dose range should beconsidered.

A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates 0-14 days that require specific dosage schedules:

Acute otitis media

For initial treatment of acute otitis media, a single intramuscular dose of Ceftriaxone 50 mg/kg canbe given.

Pre-operative prophylaxis of surgical site infections

20 - 50 mg/kg as a single pre-operative dose.

Syphilis

The generally recommended dose is 50 mg/kg once daily for 10-14 days. The doserecommendations in syphilis, including neurosyphilis, are based on very limited data. National orlocal guidance should be taken into consideration.

Duration of therapy

The duration of therapy varies according to the course of the disease. As with antibiotic therapy ingeneral, administration of ceftriaxone should be continued for 48 - 72 hours after the patient hasbecome afebrile or evidence of bacterial eradication has been achieved.

Older people

The dosages recommended for adults require no modification in older people provided that renaland hepatic function is satisfactory.

Patients with hepatic impairment

Available data do not indicate the need for dose adjustment in mild or moderate liver functionimpairment provided renal function is not impaired.

There are no study data in patients with severe hepatic impairment.

Patients with renal impairment

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxoneprovided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinineclearance < 10 ml/min) should the ceftriaxone dosage not exceed 2 g daily.

In patients undergoing dialysis no additional supplementary dosing is required following thedialysis. Ceftriaxone is not removed by peritoneal- or haemodialysis. Close clinical monitoring forsafety and efficacy is advised.

Patients with severe hepatic and renal impairment

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

Method of administration

Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route)or by slow intravenous injection over 5 minutes, or by deep intramuscular injection. Intravenousintermittent injection should be given over 5 minutes preferably in larger veins. Intravenous dosesof 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. Inneonates, intravenous doses should be given over 60 minutes to reduce the potential risk ofbilirubin encephalopathy. Intramuscular injections should be injected well within the bulk of arelatively large muscle and not more than 1 g should be injected at one site. Intramuscularadministration should be considered when the intravenous route is not possible or less appropriatefor the patient. For doses greater than 2 g intravenous administration should be used.

If lidocaine is used as a solvent, the resulting solution should never be administered intravenously.The information in the Summary of Product Characteristics of lidocaine should be considered.Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require)treatment with calcium-containing intravenous solutions, including continuous calcium-containinginfusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used toreconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administrationbecause a precipitate can form. Precipitation of ceftriaxone-calcium can also occur whenceftriaxone is mixed with calcium- containing solutions in the same intravenous administrationline. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administeredsimultaneously.

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

For instructions on reconstitution of the medicinal product before administration.

4.3 Contraindications

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactamantibacterial agent (penicillins, monobactams and carbapenems).

Ceftriaxone is contraindicated in:

Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)*

Full-term neonates (up to 28 days of age):

- withhyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these areconditions in which bilirubin binding is likely to be impaired*
- if they require (or are expected to require) intravenous calcium treatment, or calcium-containinginfusions due to the risk of precipitation of a ceftriaxonecalcium salt.

*In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin bindingsites leading to a possible risk of bilirubin encephalopathy in these patients.

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxonewhen lidocaine solution is used as a solvent. See information in the Summary of ProductCharacteristics of lidocaine, especially contraindications.

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivityreactions have been reported (see section 4.8). In case of severe hypersensitivity reactions,treatment with ceftriaxone must be discontinued immediately and adequate emergency measuresmust be initiated. Before beginning treatment, it should be established whether the patient has ahistory of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any othertype of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a historyof non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxicepidermal necrolysis) have been reported; however, the frequency of these events is not known.

Interaction with calcium containing products

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

In patients of any age ceftriaxone must not be mixed or administered simultaneously with anycalcium-containing intravenous solutions, even via different infusion lines or at different infusionsites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutionsmay be administered sequentially one after another if infusion lines at different sites are used or ifthe infusion lines are replaced or thoroughly flushed between infusions with physiological saltsolutionto avoid precipitation. In patients requiring continuous infusion with calcium-containingtotal parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the useof alternative antibacterial treatments which do not carry a similar risk of precipitation. If the useof ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutionsand ceftriaxone can be administered simultaneously, albeit via different infusion lines at differentsites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxoneinfusion and the infusion lines flushed between solutions.

Pediatric population

Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established forthe dosages described under Posology and Method of Administration. Studies have shown thatceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone is contraindicated in premature and full-term neonates at risk of developing bilirubinencephalopathy.

Immune mediated haemolyticanaemia

An immune mediated haemolyticanaemia has been observed in patients receiving cephalosporinclass antibacterials including Ceftriaxone. Severe cases of haemolyticanaemia, includingfatalities, have been reported during Ceftriaxone treatment in both adults and children.

If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associatedanaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Long term treatment

During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported withnearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to lifethreatening.Therefore, it is important to consider this diagnosis in patients who present withdiarrhoea during or subsequent to the administration of ceftriaxone (see section 4.8).

Discontinuation of therapy with ceftriaxone and the administration of specific treatmentfor Clostridium difficile should be considered. Medicinal products that inhibit peristalsis shouldnot be given.

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

Severe renal and hepatic insufficiency

In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy isadvised.

Interference with serological testing

Interference with Coombs tests may occur, as Ceftriaxone may lead to false-positive test results.Ceftriaxone can also lead to false-positive test results for galactosaemia.

Non-enzymatic methods for the glucose determination in urine may give false- positive results.Urine glucose determination during therapy with Ceftriaxone should be done enzymatically.

Sodium

Each gram of Ceftriaxone contains 3.6 mmol sodium. This should be taken into consideration inpatients on a controlled sodium diet.

Antibacterial spectrum

Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as asingle agent for the treatment of some types of infections unless the pathogen has already beenconfirmed. In polymicrobial infections, where suspected pathogens include organisms resistant toceftriaxone, administration of an additional antibiotic should be considered.

Use of lidocaine

In case a lidocaine solution is used as a solvent, ceftriaxone solutions must only be used forintramuscular injection. Contraindications to lidocaine, warnings and other relevant informationas detailed in the Summary of Product Characteristics of lidocaine must be considered before use.The lidocaine solution should never be administered intravenously.

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility ofprecipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have beendetected on sonograms of the gallbladder and have been observed more frequently at ceftriaxonedoses of 1 g per day and above. Caution should be particularly considered in the pediatricpopulation. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarelyprecipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases,conservative nonsurgical management is recommended and discontinuation of ceftriaxonetreatment should be considered by the physician based on specific benefit risk assessment.

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patientstreated with Ceftriaxone (see section 4.8). Most patients presented with risk factors for biliarystasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition.A trigger or cofactor of Ceftriaxone-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone.In symptomatic cases, sonography should be performed. Use in patients with history of renallithiasis or with hypercalciuria should be considered by the physician based on specific benefit riskassessment.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be usedto reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenousadministration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occurwhen ceftriaxone is mixed with calcium- containing solutions in the same intravenousadministration line. Ceftriaxone must not be administered simultaneously with calcium-containingintravenous solutions, including continuous calcium-containing infusions such as parenteralnutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calciumcontainingsolutions may be administered sequentially of one another if the infusion lines arethoroughly flushed between infusions with a compatible fluid. In vitro studies using adult andneonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk ofprecipitation of ceftriaxone-calcium.

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk ofbleeding. It is recommended that the International Normalised Ratio (INR) is monitored

frequentlyand the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatmentwith ceftriaxone.

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosideswhen used with cephalosporins. The recommended monitoring of aminoglycoside levels (andrenal function) in clinical practice should be closely adhered to in such cases.

In an in-vitro study antagonistic effects have been observed with the combination ofchloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

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

In patients treated with ceftriaxone, the Coombs' test may lead to false-positive test results.

Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.

Likewise, non-enzymatic methods for glucose determination in urine may yield false-positiveresults. For this reason, glucose level determination in urine during therapy with ceftriaxone shouldbe carried out enzymatically.

No impairment of renal function has been observed after concurrent administration of large dosesof ceftriaxone and potent diuretics (e.g. furosemide).

Simultaneous administration of probenecid does not reduce the elimination of ceftriaxone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use ofceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effectswith respect to embryonal/foetal, perinatal and postnatal development. Ceftriaxone should only beadministered during pregnancy and in particular in the first trimester of pregnancy if the benefitoutweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses ofceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea andfungal infection of the mucous membranes cannot be excluded. The possibility of sensitization should be taken into account. A decision must be made whether to discontinue breast-feeding orto discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feedingfor the child and the benefit of therapy for the woman.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

During treatment with ceftriaxone, undesirable effects may (occur e,g, dizziness), which mayinfluence the ability to drive and use machines. Patients should be cautious when driving oroperating machinery.

4.8 Undesirable effects

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

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

Not known (cannot be estimated from the available data)

Class	**Common**	**Uncommon**	**Rare**	**Not Known**
Infections and infestations		Genital fungal infection	Pseudo membranous colitisb	Superinfectionb
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemiab Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivityb
Nervous system disorders		Headache Dizziness		Convulsion

Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoeab Loose stools	Nausea Vomiting		Pancreatitisb Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitationb Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndromeb Toxic epidermal necrolysisb Erythema multiforme Acute generalised exanthematous pustulosis
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false Positive Galactosaemia test false positiveb

				Non enzymatic methods for glucose determination false positiveb

aBased on post-marketing reports. Since these reactions are reported voluntarily from a populationof uncertain size, it is not possible to reliably estimate their frequency which is thereforecategorised as not known.

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with Clostridium difficile.Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre- term and fulltermneonates (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 neonates is a result of their low blood volume and the longer half-lifeof ceftriaxone compared with adults.

Cases of renal precipitation have been reported, primarily in children older than 3 years of age andwho have been treated with either high daily doses (e.g. ≥ 80 mg/kg/day) or total doses exceeding10 grams and who presented with other risk factors (e.g. fluid restrictions or confinement to bed).The risk of precipitate formation is increased in immobilized or dehydrated patients. This eventmay be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversibleupon discontinuation of ceftriaxone.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patientstreated with doses higher than the recommended standard dose. In children, prospective studieshave shown a variable incidence of precipitation with intravenous application - above 30 % insome studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effectis usually asymptomatic, but the precipitations have been accompanied by clinical symptoms suchas pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases.

Precipitation is usually reversible upon discontinuation of ceftriaxone.

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrationcannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatmentof overdose should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins, ATC code: J01DD04

Mechanism of action:

Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin bindingproteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, whichleads to bacterial cell lysis and death.

Resistance

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

• Hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs),carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic

Gram-negative bacterial species.

• reduced affinity of penicillin-binding proteins for ceftriaxone.

• Outer membrane impermeability in Gram-negative organisms.

• Bacterial efflux pumps.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee onAntimicrobial Susceptibility Testing (EUCAST) are as follows:

Pathogen	**Dilution Test (MIC, mg/L)**	
	Susceptible	**Resistant**
Enterobacteriaceae	≤ 1	> 2
Staphylococcus spp.	a.	a.
Streptococcus spp. (Groups A, B, C and G)	b.	b.
Streptococcus pneumoniae	≤ 0.5c	> 2
Viridans group Streptococci	≤ 0.5	> 0.5

Haemophilusinfluenzae	≤ 0.12c	> 0.12
Moraxella catarrhalis	≤ 1	> 2
Neisseria gonorrhoeae	≤ 0.12	> 0.12
Neisseria meningitidis	≤ 0.12c	> 0.12
Non-species related	≤ 1d	> 2

a. Susceptibility inferred from cefoxitin susceptibility.

b. Susceptibility inferred from penicillin susceptibility.

c. Isolates with a ceftriaxone MIC above the susceptible breakpoint are rare and, if found, shouldbe re-tested and, if confirmed, should be sent to a reference laboratory.

d. Breakpoints apply to a daily intravenous dose of 1 g x 1 and a high dose of at least 2 g x 1.

Clinical efficacy against specific pathogens

The prevalence of acquired resistance may vary geographically and with time for selected speciesand local information on resistance is desirable, particularly when treating severe infections. Asnecessary, expert advice should be sought when the local prevalence of resistance is such that theutility of ceftriaxone in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes Staphylococcus aureus (methicillin-susceptible)£ Staphylococci coagulase-negative (methicillin-susceptible)£ Streptococcus pyogenes (Group A)
Streptococcus agalactiae(Group B) Streptococcus pneumoniae Viridans Group Streptococci Gram-negative aerobes Borreliaburgdorferi Haemophilusinfluenzae Haemophilusparainfluenzae Moraxella catarrhalis Neisseria gonorrhoea Neisseria meningitidis Proteus mirabilis

Providencia spp
Treponema pallidum
Species for which acquired resistance may be a problem
Gram-positive aerobes
Staphylococcus epidermidis+
Staphylococcus haemolyticus+
Staphylococcus hominis+
Gram-negative aerobes
Citrobacterfreundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli%
Klebsiella pneumoniae%
Klebsiellaoxytoca%
Morganellamorganii
Proteus vulgaris
Serratiamarcescens
Anaerobes
Bacteroidesspp.
Fusobacterium spp.
Peptostreptococcusspp.
Clostridium perfringens
Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.
Listeria monocytogenes
Gram-negative aerobes
Acinetobacter baumannii
Pseudomonas aeruginosa
Stenotrophomonasmaltophilia
Anaerobes
Clostridium difficile
Others:
Chlamydia spp.
Chlamydophilaspp.

Mycoplasma spp. Legionella spp. Ureaplasmaurealyticum

£ All methicillin-resistant staphylococci are resistant to ceftriaxone.

+ Resistance rates >50% in at least one region

% ESBL producing strains are always resistant

5.2 Pharmacokinetic properties

Absorption

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasmaceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion ofceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250mg/l respectively. Following intramuscular injection, mean peak plasma ceftriaxone levels areapproximately half those observed after intravenous administration of an equivalent dose. Themaximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and isreached in 2 - 3 hours after administration.

The area under the plasma concentration-time curve after intramuscular administration isequivalent to that after intravenous administration of an equivalent dose.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimalinhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart,biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostaticand synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen onrepeated administration; steady state is reached in most cases within 48 - 72 hours depending onthe route of administration.

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 tobe up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamedmeninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours afterintravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milkat low concentrations.

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasmaconcentrations below 100 mg/l. Binding is saturable and the bound portion decreases with risingconcentration (up to 85 % at a plasma concentration of 300 mg/l).

BiotransformationCeftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gutflora.

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerularfiltration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of totalceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are onlyminimally altered with the half-life slightly increased (less than two fold), even in patients withseverely impaired renal function.

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

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

Older people

In older people aged over 75 years the average elimination half-life is usually two to three timesthat of young adults.

Pediatric population

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels offree ceftriaxone may be further increased by factors such as reduced glomerular filtration andaltered 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.

Linearity/non-linearity

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 proteinbinding and is therefore observed for total plasma ceftriaxone but not for free (unbound)ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the bestcorrelation with in vivo efficacy is the percentage of the dosing interval that the unboundconcentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone forindividual target species (i.e. %T > MIC).

5.3 Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formationof concrements and precipitates in the gallbladder of dogs and monkeys, which proved to bereversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity.

Carcinogenicity studies on ceftriaxone were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazoleand aminoglycosides.

Solutions containing ceftriaxone should not be mixed with or added to other agents except thosementioned in section 6.6. In particular diluents containing calcium (e.g. Ringer's solution,Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute areconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone mustnot be mixed or administered simultaneously with calcium-containing solutions including totalparenteral nutrition.

6.3 Shelf life

Unopened: 24 months

After reconstitution: Chemical and physical in-use stability has been demonstrated for 4 days at 2-8°C. From a microbiological point of view, the product should be used immediately. If not usedimmediately, in-use storage times and conditions prior to use are the responsibility of

the user andwould not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken placein controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: do not store above 30°C. Keep container in the outer carton.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

30ml colourless glass Type I or III vial closed with rubber stoppers and aluminium caps.
10 ml plastic vial for water for injection.

6.6 Special precautions for disposal <and other handling>

Concentrations for the intravenous injection: 100 mg/ml, Concentrations for the intravenousinfusion: 50 mg/ml (Please refer to section 4.2 for further information).
Reconstitution: From the calculated dose, determine the appropriate number of vials to be used.
For the intravenous or intramuscular injection, add the recommended volume of reconstitutionsolution specified in the table below and shake well until the contents of the vial have dissolvedcompletely.
For the intravenous infusion, add 15 ml of reconstitution solution and shake well until the contentsof the vial have dissolved completely.
Draw up this 15 ml of reconstituted solution and add it to 25 ml of reconstitution fluid in aninfusion bag to prepare the patient dose (making a total volume of 40 ml reconstitution fluid asspecified in the table).

	Powder	Solution for reconstitution	Quantity of solution	Displacement volume
Intramuscular injection	1g	1% Lignocaine Hydrochloride Injection BP *	3.5 ml	0.63ml
Intravenous injection	1g	Water for Injections BP	10 ml	0.63ml
Intravenous infusion	2g	Glucose Injection BP 5% 0.9% Sodium Chloride Injection	40 ml	1.25ml

		BP Sodium Chloride and Glucose Injection BP (0.45% sodium chloride and 2.5% glucose) Dextran 6% in Glucose Injection BP 5% Hydroxyethyl starch 6-10% infusions**		

* Solutions of ceftriaxone in lignocaine should not be administered intravenously.

** Formulae; 6% infusion: 30g hydroxyethylstarch, 4.5g sodium chloride, up to 500ml Water forInjections.

10% infusion: 50g hydroxyethylstarch, 4.5g sodium chloride, up to 500ml Water for Injections.

If other infusion fluids are used, compatibility with ceftriaxone should be checked. The solutionshould be clear, do not use the solution if particles are present.

7. MARKETING AUTHORISATION HOLDER

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Date: 12.07.2023