SUMMARY OF PRODUCT CHARACTERISTICS

Ceftriaxone for Injection USP 500mg

1. NAME OF THE MEDICINAL PRODUCT

Ceftriaxone for Injection USP 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Sterile Ceftriaxone Sodium USP Eq. to
Ceftriaxone 500mg

3. PHARMACEUTICAL FORM

Dry Powder for Injection.

White to yellowish orange crystalline powder filled in transparent glass vial sealed with having20mm gray butyl rubber stopper and flip off aluminium seal.

Visual Appearance: After reconstitution the solution should be clear colour less.

4. Clinical particulars

4.1 Therapeutic indications

Ceftriaxone sodium is a broad-spectrum bactericidal cephalosporin antibiotic. Ceftriaxone is active in vitro against a wide range of Gram-positive and Gram negative organisms, which β-lactamase producing strains. Ceftriaxone is indicated in the treatment of the following infections either before the infecting organism has been identified or when known to be caused by bacteria of established sensitivity.

√ Pneumonia
√ Septicaemia
√ Meningitis
√ Skin and soft tissue infections
√ Infections in neutropenic patients
√ Gonorrhoea

Peri-operative prophylaxis of infections associated with surgery. Treatment may be started before the results of susceptibility tests are known. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration Posology

Adults and children 12 years and over:

Standard therapeutic dosage: 1g once daily.

Severe infections: 2-4 g daily, normally as a once daily dose.

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. Acute, uncomplicated gonorrhoea: One dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.
Peri-operative prophylaxis: Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided doses at different injection sites), by slow intravenous injection or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Elderly: These dosages do not require modification in elderly patients provided that renal andhepatic function are satisfactory.
In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacementof bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.

Paediatric Population
Children under 12 years
Standard therapeutic dosage: 20-50mg/kg body-weight once daily.
Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

Hepatic impairment
Available data do not indicate the need for dose adjustment in mild or moderate liverfunctionimpairment provided renal function is not impaired.
There are no study data in patients with severe hepatic impairment.

Renal impairment:
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided 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 the dialysis. Ceftriaxone is not removed by peritoneal- or haemodialysis. Close clinical monitoring for safety and efficacy is advised.

Patients with severe hepatic and renal impairment
In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safetyand efficacy is advised.

4.3 Contraindications
Hypersensitivity to the active substance, to any other cephalosporin or to any of the excipients.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of betalactam antibacterial agent (penicillins, monobactams and carbapenems). Ceftriaxone is contraindicated in:

• Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronologicalage).
• Full-term neonates (up to 28 days of age):
- with hyperbilirubinaemia, 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 ceftriaxone-calcium salt.
* In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albuminbinding sites 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.
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 hypersensitivity reactions have been reported. 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 severe 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 non-severe hypersensitivity to other beta-lactam agents.
Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal 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 premature and full-term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and
calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites areused or if the infusion lines are replaced or thoroughly

flushed between infusions with physiological salt-solution o avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions.

Paediatric population

Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described under Posology and Method of Administration. Studies have shown that ceftriaxone, 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 haemolytic anaemi*a

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone. Severe cases of haemolytic anaemia, including fatalities, have been reported during Ceftriaxone treatment in both adults and children.

If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporinassociated anaemia 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 with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftriaxone. Discontinuation of therapy with ceftriaxone and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

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

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.
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.

Sodium
Each gram of ceftriaxone sodium contains approximately 3.6 mmol sodium. This should betaken into consideration in patients on a controlled sodium diet.

Antibacterial spectrum
Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed. In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, 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 for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as 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 of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment 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 patients treated with Ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor 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 historyof renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

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 used to reconstitute Ceftriaxone vials or to further dilute a reconstituted

vial for intravenous administration because a precipitate can form.
Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium- containing solutions in the same intravenous administration line.
Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y- site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium. Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone. 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. In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

The clinical relevance of this finding is unknown There have been no reports of an interaction between ceftriaxone and oral calcium containing products 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 positive results. For this reason, glucose level determination in urine during therapy with ceftriaxone should be carried out enzymatically. No impairment of renal function has been observed after concurrent administration of large doses of 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 of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for 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 may influence the ability to drive and use machines. Patients should be cautious when driving or operating 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.
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)

System organ class	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Genital fungal infection	Pseudomembranous colitis[b]	Superinfection
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo

Respiratory,thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinaldisorders	Diarrhoea Loose stools	Nausea Vomiting		Pancreatitis Stomatitis Glossitis
Hepatobiliarydisorders	Hepatic enzyme increased			Gall bladder precipitationb Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome Toxic epidermal necrolysisb Erythema multiforme Acute generalised exanthematous pustulosis
Renal and urinarydisorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disordersand		Phlebitis Injection site pain	Odema Chills	

administration site conditions		Pyrexia		
Investigations		Blood creatinine increased		Coombs test false positive Galactosaemia test false positive Non enzymatic methods for glucose determination false positive

Description of selected adverse reactions

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.

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (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-life of ceftriaxone compared with adults.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is 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 binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads 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 Committeeon Antimicrobial 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	≤ 0.5	> 2
Viridans group Streptococci	≤0.5	>0.5
Haemophilus influenzae	≤ 0.12	> 0.12
Moraxella catarrhalis	≤ 1	> 2
Neisseria gonorrhoeae	≤ 0.12	> 0.12
Neisseria meningitidis		> 0.12

	≤ 0.12	
Non-species related	≤ 1	> 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.

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 species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility 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 StreptococciGram- negative aerobes Borrelia burgdorferi Haemophilus influenzae Haemophilus parainfluenzaeMoraxella 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 Citrobacter freundii Enterobacter aerogenes Enterobacter cloacae Escherichia coli% Klebsiella pneumoniae% Klebsiella oxytoca% Morganella morganii Proteus vulgaris Serratia marcescens Anaerobes Bacteroides spp. Fusobacterium spp. Peptostreptococcus spp.Clostridium perfringens
Inherently resistant organisms

Gram-positive aerobes Enterococcus spp. Listeria monocytogenes Gram-negative aerobes Acinetobacter baumannii Pseudomonas aeruginosa
Stenotrophomonas maltophilia Anaerobes *Clostridium* *difficile*Others: *Chlamydia* spp. *Chlamydophila* spp.*Mycoplasma* spp. *Legionella* spp. *Ureaplasma urealyticum*

5.2 Pharmacokinetic properties

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration.

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

Intravenous administration

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.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory 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, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the 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 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. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

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).

Biotransformation

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

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine,

primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two fold), even in patients with severely impaired renal function. The relatively modest increase in half-life in renal impairmentis 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.

Older people

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

Paediatric population

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.

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 protein binding 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 best correlation with in vivo efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual 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 formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. 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, fluconazole and aminoglycosides and labetalol.

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 a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition.

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store below 30°C, in a dry place, protected from light.Medicines should be kept out of the reach of children.

6.5 Nature and contents of container

1 vial of Ceftriaxone for Injection USP 500mg packed in a mono carton along with leaflet.

6.6 Special precautions for disposal and other handling

Reconstitution table Water for Injection (Intravenous Injection):

Vial size	Volume of Diluentto be added	Approx available volume	Approx displacemen tvolume
500mg	10ml	10.8ml	0.8ml

Reconstitution table1%Lidocaine Injection(Intramuscular Injection):

Vial size	Volume of Diluentto be added	Approx available volume	Approx displacemen tvolume
500mg	3.5ml	4.1ml	0.6ml

Ceftriaxone should not be mixed in the same syringe with any drug other than1% LidocaineInjection (for intramuscular injection only).

The reconstituted solution should be clear. Do not use if particles are

present.For single use only. Discard any unused contents.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Marketing Authorization Holder:

Alphaceuticals Limited
97 High Street,
Rickmansworth,
Hertfordshire, WD3 1EF
United Kingdom
+44 1923 836 379
+44 1923 840 160
marketing@neomedic.co.uk

Manufacturing Site Address:

Scott - Edil Advance Research Laboratories & Education Ltd. Hill Top Industrial Area, Bhatoli Kalan, Baddi-173205, (HP), India.Contact No: +91 – 9814433687

8. Marketing authorization number

TAN 22 HM 0090

9. Date of renewal of the authorization

Not Applicable

10. Date of revision of the text

April, 2022