Product registration dossier

Ceftriaxone for intravenous injection 1g

Submitted by

Reyoung Pharmaceutical Co., Ltd.

No.1, Ruiyang road, Yiyuan County, Shandong, P.R. China.

Module 1 :

ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Ceftriaxone for intravenous injection 1g

2. Qualitative and quantitative composition

Each vial contains: Ceftriaxone sodium equivalent to 1g of ceftriaxone.

3. Pharmaceutical form

Powder for injection

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 include 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 intravenously should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis: Usually one dose of 1g given by intravenous. In colorectal surgery, 2g should be given intravenously (in divided doses at different injection sites), in conjunction with a suitable agent against anaerobic bacteria.

Elderly: These dosages do not require modification in elderly patients provided that renal and hepatic function are satisfactory (see below).

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 liver function impairment 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 (creatinine clearance < 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 safety and efficacy 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. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions 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 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 calciumcontaining solutions in the same intravenous administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

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.

Concentrations for the intravenous injection: 100 mg/ml,

Concentrations for the intravenous infusion: 50 mg/ml

Preparation of solutions for injection and infusion

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicinal product, Chemical and physical in-use stability of the reconstituted product has been demonstrated for at least 6 hours at or below 30°C or 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

The infusion line should be flushed after each administration.

Ceftriaxone 1 g Powder for Solution for Injection or Infusion

For IV injection 1 g Ceftriaxone is dissolved in 10 ml of water for injections; which produces a clear solution. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

The displacement volume of 1 g of Ceftriaxone is 0.71 ml in water for injections. When adding 10 ml of water for injections, the final concentration of the reconstituted solution is 93.37 mg/ml.

4.3 Contraindications

Hypersensitivity to the active substance, to any other cephalosporin or to any of the excipients in the product.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial 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):

- with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*

- if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt.

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

Contraindications to lidocaine must be excluded before intravenous injection of ceftriaxone when lidocaine solution is used as a solvent. See information in the Summary of Product Characteristics 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 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 are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing 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 bilirubin encephalopathy.

Immune mediated haemolytic anaemia

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 cephalosporin-associated 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 is advised.

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 be taken 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 intravenous 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 history of 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 intravenous 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 diarrhoea 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 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)

Not known (cannot be estimated from the available data)

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known [a]**
Infections and infestations		Genital fungal infection	Pseudomembranous colitis[b]	Superinfection[b]
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[b]
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus
Skin and subcutaneous tissue	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b]

disorders				Toxic epidermal necrolysis[b] 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[b] Galactosaemia test false positive[b] Non enzymatic methods for glucose determination false positive[b]

a Based on post-marketing reports. Since these reactions are reported voluntarily from a

population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

b See section Special warnings and precautions for use

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme www.mhra.gov.uk/yellowcard.

4.8 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 Committee on 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[c.]	> 2
Viridans group Streptococci	≤0.5	>0.5
Haemophilus influenzae	≤ 0.12[c.]	> 0.12
Moraxella catarrhalis	≤ 1	> 2
Neisseria gonorrhoeae	≤ 0.12	> 0.12

Neisseria meningitidis	≤ 0.12 [c.]	> 0.12
Non-species related	≤ 1[d.]	> 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, should be 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 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 Streptococci
Gram-negative aerobes

Borrelia burgdorferi Haemophilus influenzae Haemophilus parainfluenzae 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 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

£ 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

Intravenous administration

Following intravenous 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 intravenous 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 intravenous administration is equivalent to that after intravenous administration of an equivalent dose.

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 (C_{max}) 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 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.

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.

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

Three years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Ceftriaxone is supplied in 10ml mould vial, butyl rubber and flip off caps.

The vials are packed in boxes of 1vial with 1 ampoule of water for injection (10ml).

7. Marketing authorisation holder

Nkoyo Chemists Limited

12, Nwaka-Nwa street, Independence Lay out, Enugu, Nigeria.