1.3.1 Summary of Product Characteristics (SmPC)

Please see the following page.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceftriaxone sodium for injection 1.0g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftriaxone sodium equivalent to 1 g ceftriaxone.
Each gram of ceftriaxone sodium contains approximately 3.6 mmol (82.8 mg) sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection
A white or almost white crystalline powder, odorless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by pathogens sensitive to ceftriaxone, e.g.: Sepsis; Meningitis; Disseminated Lyme borreliosis (early (stage II) and late (stage III)); Abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts); Infections of the bones, joints, soft tissue, skin and of wounds; Infections in patients with impaired defense mechanisms; Renal and urinary tract infections; Respiratory tract infections, particularly pneumonia, and ear, nose and throat infections; Genital infections, including gonorrhea; Perioperative prophylaxis of infections.

4.2 Posology and method of administration

Posology

Adults and children over 12 years

The usual dosage is 1 to 2 g Ceftriaxone Injection once daily (every 24 hours). In severe cases or in
infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for once daily administration:
Neonates (up to 14 days): 20 to 50 mg/kg bodyweight once daily, the daily dose should not exceed 50 mg/kg. Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age). The medication safety for neonates (birth weight less than 2kg) is still under evaluation.Administrate cautiously or avoid using this product in neonates with jaundice or strong tendency of jaundice.
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 parental nutrition because of the risk of precipitation of ceftriaxone-calcium salt.
Infants and children (15 days to 12 years): 20 to 80 mg/kg bodyweight once daily.

For children with bodyweights of 50 kg or more, the usual adult dosage should be used.
Intravenous doses of not less than 50 mg/kg bodyweight should be given by infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Elderly

The dosages recommended for adults require no modification in elder people provided that renal and hepatic function is satisfactory.

Duration of therapy

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.

Combination therapy

Synergy between ceftriaxone and aminoglycosides has been demonstrated with many Gram negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life threatening infections due to micro-organisms such as *Pseudomonas aeruginosa*. To avoid an incompatibility reaction, the two medicines must be administered separately at the recommended dosages.
Ceftriaxone is not compatible with amsacrine, vancomycin and fluconazole during intravenous administration.

Special dosage instructions

Meningitis

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

Neisseria meningitidis	4 days;
Haemophilus influenzae	6 days;
Streptococcus pneumoniae	7 days.

Lyme disease

50mg/kg once daily for 14days. The maximum daily dose is 2g.

Gonorrhoea

For penicillinase-producing and non-penicillinase-producing strains, give a single intramuscular dose of 250 mg.

Perioperative prophylaxis

A single dose of 1 to 2 g depending on the risk of infection given at 30 to 90 minutes prior to surgery. In colorectal surgery, administration of Ceftriaxone Injection with or without a 5-nitroimidazole, e.g. ornidazole (separate administration, refer to Administration) has proven effective.

Patients with 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.

Patients with hepatic impairment

In patients with impaired hepatic function, there is no need to reduce the dosage of ceftriaxone provided renal function is not impaired.

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

As a general rule, the solution should be used immediately after preparation. Reconstituted solutions retain their physical and chemical stability for six hours at room temperature or 24 hours under refrigeration (2-8 °C). The solutions range in colour from pale yellow to amber, depending on the concentration and the length of storage. This characteristic of the active ingredient is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection

For intramuscular injection, dissolve Ceftriaxone Injection 0.5 g in 2 ml, and Ceftriaxone Injection 1 g in 3.5 ml lidocaine hydrochloride solutions 1% w/v and inject well within the body of a relatively large muscle. It is recommended not to inject more than 1 g at one site. Never administer the lidocaine solution intravenously.

Intravenous injection

For intravenous injection, dissolve Ceftriaxone Injection 0.5 g in 5 ml, and Ceftriaxone Injection 1 g in 10 ml water for injections. The intravenous administration should be given over 2 to 4 minutes.

Intravenous infusion

The infusion should be given over at least 30 minutes. For intravenous infusion, dissolve Ceftriaxone Injection 2 g in 40 ml of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl starch 6 to 10%, water for injections. Ceftriaxone solutions may be incompatible with other medicines or diluents and should not be mixed with or piggybacked into solutions or diluents containing antibiotics or solutes different to those listed above.

4.3 Contraindications

Hypersensitivity reactions

Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone or the excipients or to the cephalosporin class of antibiotics. In patients hypersensitive to penicillin or any other type of beta-lactam antibacterial agent, the possibility of allergic cross-reactions should be borne in mind.

Lidocaine

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent. Refer to the contraindications of lidocaine. Ceftriaxone solutions containing lidocaine should never be administered intravenously.

Premature neonates

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

Hyperbilirubinemic Neonates

Ceftriaxone is contraindicated in hyperbilirubinemic neonates. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Neonates

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 parental nutrition because of the risk of precipitation of ceftriaxone-calcium salt.

4.4 Special warnings and precautions for use

Warnings

(1) This product should be administered under the guidance of a professional physician, and the hospital can take emergency measures for allergic reactions. Before using this product, the medical history should be inquired in detail, including the hypersensitivity reactions to penicillins, cephalosporins and any other drugs, allergy constitution (such as the history of anaphylactic shock, allergic asthma, allergic rhinitis, urticaria and other diseases), family history, etc. This product should be used with caution in patients with a history of hypersensitivity, especially for drugs, see the contraindication section. Patients with penicillin anaphylactic shock should not use cephalosporins. After administration, especially for the first medication, the patients should stay inhospital for close observation within 30 minutes, and given emergency treatment in time if anaphylactic shock occurs. Like other cephalosporin antibiotics, there are fatal reports of allergic reactions, even if the allergy history or the use of the product is unknown.

(2) Superinfection: As with other antibacterial agents, superinfection caused by ceftriaxone non-susceptible microorganisms may occur after ceftriaxone administration.

(3) 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.

(4) Clostridium difficile-associated diarrhea: Clostridium difficile-associated diarrhea (CDAD) has been reported with many antibiotics including ceftriaxone. The severity of the colitis may range from mild to life threatening. Antibiotic treatment altered the normal flora of the colon, which resulting in overgrowth of *Clostridium difficile*.

Clostridium difficile produces toxin A and B, toxin A and B promote the development of CDAD. Toxin high-yielding *Clostridium difficile* strains increase morbidity and mortality because such infections are refractory to antibiotics and may require colonic resection. The possibility of CDAD must be considered in all patients who present with diarrhea after using antibiotics.

Medical history should be inquired carefully, as CDAD was reported to appear after two months of antibiotic therapy.

If CDAD is suspected or confirmed, the therapy with antibiotics with no effect on *Clostridium difficile* should be discontinued. Fluid and electrolyte handling, protein supplement, appropriate antibiotic therapy against *C. difficile*, and surgical evaluation should be provided according to the clinical situation.

(5) As with other cephalosporins, ceftriaxone may cause gastrointestinal disorders such as diarrhea and pseudomembrane colitis, therefore, the changes of the disease should be closely monitored for the patients with a history of gastrointestinal diseases.

(6) Precipitates of calcium ceftriaxone: The precipitates of calcium ceftriaxone 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.

There are no reports to date of intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions. However, ceftriaxone and calcium-containing solutions should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines.

(7) Paediatric population: Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established 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 neonates (especially prematures) at risk of developing bilirubin encephalopathy.

(8) Haemovigilance: During prolonged treatment complete blood count should be performed at regular intervals.

(9) Pancreatitis, possibly of biliary obstruction aetiology, has been rarely 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 co-factor role of ceftriaxone-related biliary precipitation cannot be discounted.

Drug abuse and dependence

Not applicable.

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.

Influence on diagnostic tests

A false positive Coomb's test result has been rarely observed in patients treated with ceftriaxone. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosemia.

Likewise, nonenzymatic methods for the glucose determination in urine may give false-positive results. Select enzymatic reagents for urinary glucose determination during ceftriaxone therapy.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

The elimination of ceftriaxone is not altered by probenecid. In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

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 the anti-vitamin K drug may increase 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.

Ceftriaxone is not compatible with amsacrine, vancomycin and fluconazole during the intravenous administration.

4.6 Fertility, pregnancy and lactation

Ceftriaxone should only be administered if the benefit outweighs the risk.

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive toxicity studies have been performed in animals, and have not shown evidence of embryotoxocity, foetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or peri- and postnatal development. In primates, no embryotoxicity or teratogenicity was demonstrated.

As ceftriaxone is secreted in the breast milk at low concentrations, caution is advised in nursing mothers.

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

Clinical trials

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 to < 1/10)

Uncommon (≥ 1/1000 to < 1/100)

Rare (≥ 1/10000 to < 1/1000)

System Organ Class	**Common**	**Uncommon**	**Rare**
Infections and infestations		Genital fungal infection	Pseudomembranous Colitis
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy	
Nervous system disorders		Headache Dizziness	
Respiratory, thoracic and mediastinal disorders			Bronchospasm
Gastrointestinal disorders	Diarrhoea Loose stools	Nausea Vomiting	
Hepatobiliary disorders	Hepatic enzyme increased		
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria
Renal and urinary			Haematuria

System Organ Class	Common	Uncommon	Rare
disorders			Glycosuria
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills
Investigations		Blood creatinine increased	

Post-marketing

The following adverse reactions are found during the post-marketing of ceftriaxone. Since these reactions are reported from a population of uncertain size, it is not possible to reliably estimate their frequency and /or determine its causal relationship with drug exposure.

Systemic side effects

Gastrointestinal disorders: pancreatitis, stomatitis and glossitis.

Hematological abnormalities: isolated cases of agranulocytosis (<500 / mm^3) have been reported, most of which occurred after 10 days of treatment at a total dose of more than 20g.

Skin disorders: Isolated cases of acute generalized exanthematous pustulosis (AGEP) and severe skin reactions (erythema multiforme, StevensJohnson syndrome, or Lyell syndrome / Toxic epidermal necrolysis) have been reported.

Nervous system disorders: Convulsion

Infections and infestations: Superinfection

Other rare side effects

Precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reaction.

Interaction with the calcium

Two *in vitro* studies evaluated the interaction of ceftriaxone and calcium, one using adult plasma and the other using neonatal cord plasma. The maximum concentration of ceftriaxone was 1 mM (exceeding the plasma concentration obtained after administrating ceftriaxone 2g for more than 30 minutes) and the maximum calcium concentration was 12 mM (48 mg/dL). The recovery of ceftriaxone is reduced when the calcium concentration in adult plasma of 6 mM (24 mg/dL) or higher, and the calcium concentration in neonatal plasma of 4 mM (16 mg/dL) or higher. This suggests that ceftriaxone-calcium precipitate may be produced.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in neonates have been described. Some of them had received ceftriaxone and calcium through the same intravenous line, and precipitate had been observed in the intravenous line in some cases. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. An autopsy of this neonate revealed no crystalline substance. Other than

neonates, there are no similar reports in other patients.

Cases of renal precipitation have been reported, mostly in children who have been treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. fluid restrictions or confinement to bed). This event may be asymptomatic or symptomatic, and may lead to renal insufficiency and anuria, but is reversible upon discontinuation of ceftriaxone.

Local side effects

Phlebitis at the site of injection occur rarely. These may be minimized by slow (two to four minutes) injection of the substance.

Diagnostic tests

Coomb's test, galactosemia test and nonenzymatic methods for the glucose determination may give false-positive results.

4.9 Overdose

In the case of overdosage, drug concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mode 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.

Ceftriaxone remains active in the presence of certain β -lactamases (including penicillinase and cephalosporinases) in Gram-positive and Gram-negative bacteria.

The main ceftriaxone-resistance mechanisms: hydrolysis of β-lactamase, change of penicillin-binding proteins (PBPs), and decreased membrane permeability.

Interaction with other antimicrobial agents:

In vitro studies, chloramphenicol and ceftriaxone were antagonism.

Ceftriaxone is usually active against most of the following microorganisms in vitro and in clinical infections.

Gram-negative aerobes:

Acinetobacter acetate, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella, Klebsiella pneumonia,

Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus, Proteus vulgaris, Pseudomonas aeruginosa, Serratia marcescens

Gram-positive aerobes:

Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans

Anaerobic organisms:

Bacteroides fragilis, Clostridium, Peptostreptococcus

The following *in vitro* test data are available, but their clinical significance is unclear. At least 90% of the following organisms have a minimum inhibitory concentration (MIC value) less than or equal to the susceptible breakpoint of ceftriaxone in vitro . However, data on the effectiveness of ceftriaxone for clinical infections caused by these microorganisms have not been obtained in sufficient and well-controlled clinical trials.

Gram-negative aerobes:

Citrobacter, Citrobacter freundii, Provedensis, Salmonella (including Salmonella typhi), Shigella

Gram-positive aerobes:

Streptococcus agalactiae

Anaerobic organisms:

Porphyromonas melanogen (Bacteroides), Prevotella bivia (Bacteroides)

Susceptibility test method

Where possible, the clinical microbiology laboratory should regularly report to the doctor and provide the relevant *in vitro* susceptibility test results of the antimicrobial drugs used in the hospital, which can reflect the susceptibility characteristics of the hospital and community-acquired pathogens. These reports can help physicians to choose antimicrobial agents during treatment.

Dilution method

Determine the minimum inhibitory concentration (MIC) values by quantitative method, the MIC can be used to assess the susceptibility of bacteria to antimicrobial agents. MIC shall be determined using standardized techniques (broth or agar) and the MIC values may be interpreted according to the criteria in Table 2.

Diffusion method

The quantitative determination of the inhibition zone diameter also allows for the reproducible estimation of bacterial susceptibility to antimicrobial agents. The size of the inhibition zone represents the degree of bacterial susceptibility to antimicrobial agents and should be determined using standardized techniques. Determine the bacterial susceptibility to antimicrobial drugs using disk with 30μg of ceftriaxone, and judge the diffusion according to the criteria in Table 2.

Anaerobic method

For anaerobic bacteria, the minimum inhibitory concentration (MIC) of ceftriaxone susceptibility test can be detected by the standard agar diffusion method. The minimum inhibitory values obtained should be determined according to the criteria described in Table 2.

Table 2 The interpretative criteria for susceptibility to ceftriaxone

Pathogen	MIC（mg/L）			Inhibition zone diameter（mm）		
	Susceptible（S）	Intermediate susceptible（I）	Resistant（R）	Susceptible（S）	Intermediate susceptible（I）	Resistant（R）
Enterobacteriaceae[a]	≤1	2	≥4	≥23	20~22	≤19
Haemophilus influenzae[b,c]	≤2	---	---	≥26	---	---
Neisseria gonorrhoeae[a]	≤0.25	---	---	≥35	---	---
Neisseria meningitidis	≤0.12	---	---	≥34	---	---
Streptococcus pneumoniae[d] meningitis isolates	≤0.5	1	≥2	---	---	---
Streptococcus pneumoniae[d] non-meningitis isolates	≤1	2	≥4	---	---	---
Streptococcus spp. *β-haemolytic*[c]	≤0.5	---	---	≥24	---	---
Streptococcus viridans	≤1	2	≥4	≥27	25~26	≤24
Anaerobic bacteria (agar method)	≤1	2	≥4	---	---	---

[a]The interpretation criteria for susceptibility of *Enterobacteriaceae* is based on intravenous injection of 1g every 24 hours. For moderately susceptible isolates, the patients with normal renal function are intravenously injected 2g every 24 hours.

[b]The interpretation criteria for susceptibility of H. influenzae is based on intravenous injection of 2g every 24 hours in patients with normal renal function.

[c]Lack of available data for resistant bacteria other than the "Susceptible" results. If isolates with a MIC results other than "Susceptible" are found, should be sent to a reference laboratory for additional testing .

[d]The disk diffusion method is not suitable for testing the susceptibility of *S. pneumoniae* to ceftriaxone. However, *pneumococci* with oxacillin inhibition zone diameter >20mm are susceptible to penicillin (MIC≤0.06mg/L). The susceptibility of *S. pneumoniae* to penicillin

(ceftriaxone) cannot be determined to be resistant or intermediate susceptible only based on the oxacillin inhibition zone diameter ≤19mm.

The susceptibility of *Staphylococcus* to ceftriaxone may be presumably derived from the tests of penicillin and cefoxitin / oxacillin.

The "susceptible" indicates that if the antimicrobial drug reaches an effective concentration at the site of infection, the pathogen growth is most likely inhibited. The"intermediate susceptible" indicates that the results are ambiguous and the test should be repeated if the organism is not fully susceptible to replaceable clinically viable drugs. This classification also provides a buffer space to prevent explanatory differences resulting from small, uncontrolled technical factors, and the "resistant" indicates that other treatments should be taken if the antimicrobial drug reaches an effective concentration at the infection site and most likely fails to inhibit the growth of the pathogen.

Quality control

Standardized susceptibility testing methods require laboratory reference product to monitor and ensure the samples and reagents used in the susceptibility testing and the accuracy and precision of the techniques of the test operator.

Ceftriaxone reference standards with the MIC values shown in Table 3 shall be provided. The inhibition zone diameter for disk with 30μg ceftriaxone using diffusion method should meet the values given in Table 3.

Table 3 Acceptable quality control range for ceftriaxone

Quality control strains	MIC (mg/L)	Inhibition zone diameter (mm)
Escherichia coli ATCC25922	0.03-0.12	29-35
Staphylococcus aureus ATC23923	-----	22-28
Staphylococcus aureus ATCC29213	1-8	-----
Haemophilus influenzae ATCC49247	0.06-0.25	31-39
Neisseria gonorrhoeae ATCC49226	0.004-0.015	39-51
Pseudomonas aeruginosa ATCC27853	8-64	17-23
Streptococcus pneumoniae ATCC49619	0.03-0.12	30-35
Bacteroides fragilis ATCC25285 (Agar method)	32-128	-----
Bacteroid ATCC29741 (Agar method）	64-256	-----

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are nonlinear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, and lower than the proportion of dose increases. The nonlinearity is due to saturation of plasma protein binding, so the total plasma ceftriaxone show nonlinearity, not for the free (unbound) ceftriaxone.

Absorption

The maximum plasma concentration after a single IM 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 IM

administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone.

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. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose.

Distribution

The volume of distribution of ceftriaxone is 7-12 L. Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2 g; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids. Following intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, sustaining bactericidal concentrations against susceptible organisms for 24 hours.

Protein binding

Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in the concentration, e.g. from 95% binding at plasma concentrations of <100 mg/L to 85% binding at 300 mg/L.

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.

Metabolism

Ceftriaxone is not metabolized systemically; only the intestinal flora transforms the agent into inactive metabolites.

Elimination

The total plasma clearance is 10 – 22 mL/min. Renal clearance is 5 – 12 mL/min. 50-60% of ceftriaxone is excreted unchanged in the urine, while 40-50% is excreted unchanged in the bile. The elimination half-life in adults is about eight hours.

Special populations

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.

Elderly

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

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.

5.3 Preclinical safety data

Inherent toxicity

Ceftriaxone Ames test, micronucleus test, and in vitro cultured human lymphocytes chromosome aberration test are all negative.

Reproduction toxicity

Intravenous administration of ceftriaxone 586mg/kg/ day (about 20 times the clinical recommended dose of 2g/ day) had no effect on the fertility of rats.

Reproductive toxicity tests show that there was no embryotoxicity, fetal toxicity and teratogenicity observed in mice and rats at 20 times the normal human dose. No embryotoxicity or teratogenicity was observed in nonhuman primates at about 3 times the human dose.

In Stage I (fertility and general reproductive toxicity) and Stage Ⅲ (perinatal toxicity) studies, rats were given ceftriaxone IV in a dose of 586mg/kg/day or lower, it did not show significant effects on each reproductive indicators (including postpartum development, functional behavior and offspring fertility) during pregnancy and lactation period.

Other toxicity

Ceftriaxone-calcium salt precipitate was found in the gallbladder bile of dogs (given ceftriaxone 100mg/kg/ day for 4 weeks) and baboons (given ceftriaxone ≥335mg/kg/day for 6 months) . This phenomenon is relatively rare in humans because ceftriaxone has a longer plasma half-life in humans, ceftriaxone calcium salts are more soluble in human gallbladder bile, and the calcium content in human gallbladder bile is relatively low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

For reconstitution diluent: 10ml sterile water for injection

6.2 Incompatibilities

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

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned 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 a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition.

If treatment with a combination of another antibiotic with ceftriaxone is intended, administration should not occur in the same syringe or in the same infusion solution.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Airtight, preserve from light, store in a dry and cool place (not exceeding 30℃).

6.5 Commercial presentation

Ceftriaxone sodium 1.0g. Antibiotic vials, 1.0g/vial, 1vial/box, 10 vials/box or 50vials/box.

6.6 Special precautions for disposal

Intramuscular injection

For intramuscular injection, dissolve Ceftriaxone Injection 0.5 g in 2 ml, and Ceftriaxone Injection 1 g in 3.5 ml lidocaine hydrochloride solutions 1% w/v and inject well within the body of a relatively large muscle. It is recommended not to inject more than 1 g at one site. Never administer the lidocaine solution intravenously.

Intravenous injection

For intravenous injection, dissolve Ceftriaxone Injection 0.5 g in 5 ml, and Ceftriaxone Injection 1 g in 10 ml water for injections. The intravenous administration should be given over 2 to 4 minutes.

Intravenous infusion

The infusion should be given over at least 30 minutes. For intravenous infusion, dissolve Ceftriaxone Injection 2 g in 40 ml of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxyethyl starch 6 to 10%, water for injections. Ceftriaxone solutions may be incompatible with other medicines or diluents and should not be mixed with or piggybacked into

solutions or diluents containing antibiotics or solutes different to those listed above.
As a general rule, the solution should be used immediately after preparation. Reconstituted solutions retain their physical and chemical stability for six hours at room temperature or 24 hours under refrigeration (2-8 °C). The solutions range in colour from pale yellow to amber, depending on the concentration and the length of storage. This characteristic of the active ingredient is of no significance for the efficacy or tolerance of the drug.

7 MARKETING AUTHORISATION HOLDER

Grace Pharmacare Ltd
1A Ogunlana Drive Surulere, Lagos – Nigeria
+234 809 0666298, +234 810 4638301
grace_drugs@hotmail.com
www.gracegroup.com.ng

8 MANUFACTURING SITE AND ADDRESS

Shandong Lukang Pharmaceutical Co. Ltd.
Address: 88 Deyuan Road, High-Tech Zone, Jining, Shandong, P.R.China

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT