Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

SANAXONE 1000 (Ceftriaxone for injection 1000mg)

2. Qualitative and quantitative composition

Each vial Contains: Sterile Ceftriaxone sodium..... Equivalent to 1000mg anhydrous Ceftriaxone

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Dry powder for Injection

Description: Sterile white to yellowish orange crystalline powder, distributed in sealed containers and which when shaken with prescribed volume of sterile liquid, rapidly form clear and particle free solution.

4. Clinical particulars

4.1 Therapeutic indications

Before instituting treatment with Ceftriaxone, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone and other antibacterial drugs, Ceftriaxone should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Ceftriaxone is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis* or *Serratia marcescens.*

ACUTE BACTERIAL OTITIS MEDIA caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase

producing strains) or *Moraxella catarrhalis* (including beta-lactamase producing strains).

NOTE: In one study lower clinical cure rates were observed with a single dose of Ceftriaxone compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose ceftriaxone and the comparator. The potentially lower clinical cure rate of should be balanced against the potential advantages of parenteral therapy.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes*, Viridans group streptococci, *Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii,* Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis** or *Peptostreptococcus* species.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii* or *Klebsiella pneumoniae.*

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae,* including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of *Neisseria gonorrhoeae.*

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae.* Rocephin, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

BACTERIAL SEPTICEMIA caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae* or *Klebsiella pneumoniae.*

BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* or *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium* species (Note: most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus* species.

MENINGITIS caused by *Haemophilus influenzae, Neisseria meningitidis* or *Streptococcus pneumoniae.* Ceftriaxone has also been used

successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis*∗ and *Escherichia coli.*∗

∗Efficacy for this organism in this organ system was studied in fewer than ten infections.

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 gm dose of Ceftriaxone may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (eg, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high- risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (eg, during coronary artery bypass surgery). Although Ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

When administered prior to surgical procedures for which it is indicated, a single 1 gm dose of Ceftriaxone provides protection from most infections due to susceptible organisms throughout the course of the procedure.

4.2 Posology and method of administration

Ceftriaxone may be administered intravenously or intramuscularly.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.

Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y- site. However, in patients other than neonates, 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.

There have been no reports of an interaction between ceftriaxone and oral calcium- containing products or interaction between

intramuscular ceftriaxone and calcium- containing products (IV or oral).

NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone. It is contraindicated in premature neonates.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium- containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium.

Intravenous doses should be given over 60 minutes in neonates to reduce the risk of bilirubin encephalopathy.

PEDIATRIC PATIENTS: For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.

For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended.

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

ADULTS: The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended.

Generally, Ceftriaxone therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function.

The dosages recommended for adults require no modification in elderly patients, up to 2 gm per day, provided there is no severe renal and hepatic impairment.

Method of administration

Intramuscular Administration*:* Reconstitute Ceftriaxone powder with the appropriate diluent .

Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal total labeled dose.

After reconstitution, each 1 mL of solution contains approximately 250 mg or 350 mg equivalent of ceftriaxone according to the amount of diluent indicated below. If required, more dilute solutions could be utilized.

As with all intramuscular preparations, Ceftriaxone should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Vial Dosage Size	Amount of Diluent to be Added
500mg	250 mg/mL add 1.8 mL & 350 mg/mL add 1.0 mL
1gm	250 mg/mL add 3.6 mL & 350 mg/mL add 2.1 mL

Intravenous Administration*:* Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes, except in neonates where administration over 60 minutes is recommended to reduce the risk of bilirubin encephalopathy. Concentrations between

10 mg/mL and 40 mg/mL are recommended; however, lower concentrations may be used if desired. Reconstitute vials with an appropriate IV diluent.

Vial Dosage Size	Amount of Diluent to be Added
500mg	4.8 mL
1gm	9.6 mL

After reconstitution, each 1 mL of solution contains approximately 100 mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent.

NOTE: Parenteral drug products should be inspected visually for particulate matter before administration.

4.3 Contraindications

Hypersensitivity

Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam antibacterial agents may be at greater risk of hypersensitivity to ceftriaxone.

Neonates

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

Hyperbilirubinemic neonates: Hyperbilirubinemic neonates should not be treated with Rocephin. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.

Neonates Requiring Calcium Containing IV Solutions

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium- containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium.

Cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Rocephin and calcium- containing fluids.

In some of these cases, the same intravenous infusion line was used for both Ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. There have been no similar reports in patients other than neonates.

Lidocaine

Intravenous administration of ceftriaxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with ceftriaxone for intramuscular injection, exclude all contraindications to lidocaine. Refer to the prescribing information of lidocaine.

4.4 Special warnings and precautions for use

Hypersensitivity Reactions

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins and other beta-lactam agentsor other drugs. This product should be given cautiously to penicillin and other beta-lactam agent-sensitive patients. Antibacterial drugs should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions (i.e., anaphylaxis) have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated.

Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium- containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, 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.

Clostridium difficile -Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Hemolytic Anemia

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

Development of Drug-resistant Bacteria

Prescribing Ceftriaxone. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Patients with Renal or Hepatic Impairment

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone are administered.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the Rocephin dosage should not exceed 2 gm daily.

Ceftriaxone is not removed by peritoneal- or hemodialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

Effect on Prothrombin Time

Alterations in prothrombin times have occurred in patients treated with Ceftriaxone. Monitor prothrombin time during Ceftriaxone treatment in patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition). Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Concomitant use of ceftriaxone with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone.

Gallbladder Pseudolithiasis

Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving Ceftriaxone. These precipitates appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of gallbladder disease. The condition appears to be reversible upon discontinuation of ceftriaxone sodium and institution of conservative management. Discontinue ceftriaxone sodium in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Urolithiasis and Post-Renal Acute Renal Failure

Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving Ceftriaxone and may be detected as sonographic abnormalities. The probability of such precipitates

appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of urolithiasis, and ureteral obstruction and post-renal acute renal failure. The condition appears to be reversible upon discontinuation of ceftriaxone sodium and institution of appropriate management. Ensure adequate hydration in patients receiving Ceftriaxone. Discontinue Ceftriaxone in patients who develop signs and symptoms suggestive of urolithiasis, oliguria or renal failure and/or the sonographic findings described above.

Pancreatitis

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported in patients treated with Ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of Ceftriaxone -related biliary precipitation cannot be ruled out.

Jarisch-Herxheimer reaction (JHR)

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone, particularly in elderly patients with severe renal impairment or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ceftriaxone should be considered.

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.

Ceftriaxone has been shown to be compatible with Flagyl® IV (metronidazole hydrochloride). The concentration should not exceed 5 to 7.5 mg/mL metronidazole hydrochloride with ceftriaxone 10

mg/mL as an admixture. The admixture is stable for 24 hours at room temperature only in 0.9% sodium chloride injection or 5% dextrose in water (D5W). No compatibility studies have been conducted with the Flagyl® IV RTU® (metronidazole) formulation or using other diluents. Metronidazole at concentrations greater than 8 mg/mL will precipitate. Do not refrigerate the admixture as precipitation will occur.

Vancomycin, amsacrine, aminoglycosides, and fluconazole are incompatible with ceftriaxone in admixtures. When any of these drugs are to be administered concomitantly with ceftriaxone by intermittent intravenous infusion, it is recommended that they be given sequentially, with thorough flushing of the intravenous lines (with one of the compatible fluids) between the administrations.

Rocephin solutions should *not* be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility.

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.

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.

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.

Influence on Diagnostic Tests*:* In patients treated with ceftriaxone the Coombs' test may become positive. ceftriaxone, like other antibacterial drugs, may result in positive test results for galactosemia.

Nonenzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Rocephin 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.

4.6 Fertility, pregnancy, and lactation

Pregnancy
Pregnancy Category B on Teratogenic effects

Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

Lactation

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/avoid ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman

Fertility

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

4.7 Effects on ability to drive and use machines.

Ceftriaxone has been associated with dizziness, which may affect the ability to drive or operate machinery.

4.8 Undesirable effects

The undesirable effects usually are mild and short-term.

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (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 newborns is due to their low blood volume and the longer half life of ceftriaxone compared with adults (see sections 4.3, 4.4 and 5.2).

Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines.

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known** [a]
Infections and infestations		Genital fungal infection	Pseudo-membranous 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] Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache Dizziness	Encephalopathy	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 disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS)[b]
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

Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

4.9 Overdose

In the case of overdosage, nausea, vomiting and diarrhoea can occur. Ceftriaxone drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-bacterial for systemic use**,**third generation cephalosporin**,** 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.

Mechanism of Resistance

Resistance to ceftriaxone is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Interaction with Other Antimicrobials
In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Ceftriaxone has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections:

• Gram-negative bacteria

Acinetobacter calcoaceticus, Enterobacter aerogenes, Enterobacter cloacae Escherichia coli Haemophilus influenzae Haemophilus parainfluenzae Klebsiella oxytoca Klebsiella pneumoniae Moraxella catarrhalis Morganella morganii Neisseria gonorrhoeae Neisseria meningitidis Proteus mirabilis Proteus vulgaris Pseudomonas aeruginosa Serratia marcescens

Gram-positive bacteria

Staphylococcus aureus Staphylococcus epidermidis Streptococcus pneumoniae Streptococcus pyogenes Viridans group streptococci

• Anaerobic bacteria

Bacteroides fragilis Clostridium species Peptostreptococcus species

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftriaxone. However, the efficacy of ceftriaxone in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

• Gram-negative bacteria

Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*) *Salmonella* species (including *Salmonella typhi*) *Shigella* species

• Gram-positive bacteria

Streptococcus agalactiae

• Anaerobic bacteria

Porphyromonas (Bacteroides) melaninogenicus Prevotella (Bacteroides) bivius

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 (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).

Pharmacokinetics in the Middle Ear Fluid: In one study, total ceftriaxone concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of ceftriaxone. Mean (± SD) ceftriaxone levels in the middle ear reached a peak of 35 (± 12) μg/mL at 24 hours, and remained at 19 (± 7) μg/mL at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown.

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

5.3 Preclinical safety data

Carcinogenesis*:* Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis*:* Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured in vitro with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

6. Pharmaceutical particulars

6.1 List of excipients

Maize starch
Sodium lauryl sulphate
Croscarmellose sodium
Magnesium Stearate

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 bottles or to further dilute a reconstituted vial or bottle 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:

Ceftriaxone sterile powder should be stored below 30 °C and protected from light. After reconstitution, protection from normal light is not necessary.

Ceftriaxone *intramuscular* solutions remain stable (loss of potency less than 10%) for the following time periods:

Diluent	Concentration mg/ml	Storage Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water for Injection	100	2 days	10 days
	250, 350	24 hours	3 days
0.9% Sodium Chloride Solution	100	2 days	10 days
	250, 350	24 hours	3 days
5% Dextrose Solution	100	2 days	10 days
	250, 350	24 hours	3 days
Bacteriostatic Water + 0.9% Benzyl Alcohol	100	24 hours	10 days
	250, 350	24 hours	3 days
1% Lidocaine Solution (without epinephrine)	100	24 hours	10 days
	250, 350	24 hours	3 days

Ceftriaxone *intravenous* solutions, at concentrations of 10, 20 and 40 mg/mL, remain stable(loss of potency less than 10%) for the following time periods stored in glass or PVC containers:

Diluent	Stor ge Room Temp. (25°C)	Refrigerated (4°C)
Sterile Water	2 days	10 days
0.9% Sodium Chloride Solution	2 days	10 days
5% Dextrose Solution	2 days	10 days
10% Dextrose Solution	2 days	10 days
5% Dextrose + 0.9% Sodium Chloride Solution□	2 days	Incompatible
5% Dextrose + 0.45% Sodium Chloride Solution	2 days	Incompatible

□Data available for 10 to 40 mg/mL concentrations in this diluent in PVC containers only.

The following intravenous Ceftriaxone solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/mL and 40 mg/mL: Sodium Lactate (PVC container), 10% Invert Sugar (glass container), 5% Sodium Bicarbonate (glass container),

Freamine III (glass container), Normosol-M in 5% Dextrose (glass and PVC containers), Ionosol-B in 5% Dextrose (glass container), 5% Mannitol (glass container), 10% Mannitol (glass container).

After the indicated stability time periods, unused portions of solutions should be discarded.

Ceftriaxone reconstituted with 5% Dextrose or 0.9% Sodium Chloride solution at concentrations between 10 mg/mL and 40 mg/mL, and then stored in frozen state (-20°C)in PVC or polyolefin containers, remains stable for 26 weeks.

Frozen solutions of Ceftriaxone should be thawed at room temperature before use. After thawing, unused portions should be discarded. **DO NOT REFREEZE.**

6.5 Nature and contents of container

10 ml USP Type III clear glass vials sealed with 20 mm Grey Butyl rubber stopper and 20 mm colored flip off aluminum seal (Taxim Blue). The drug product is available in mono pack (1's) containing 01 vial in a Carton along with Sterile water for injection and Package Insert .

6.6 Special precautions for disposal and other handling:

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. Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Hydrochloride solution (for intramuscular injection only). The infusion line should be flushed after each administration

Reconstitution:
Ceftriaxone for Injection is found to be compatible with the following diluents:

1. Sterile Water for Injection
2. 0.9% Sodium chloride
3. 5% Dextrose
4. 10% Dextrose
5. 5% Dextrose +0.9 % Sodium chloride solution
6. 5% Dextrose +0.45 % Sodium chloride solution
7. 2.5% Dextrose +0.45 % Sodium chloride solution
8. 1% Lidocaine

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. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

For IM injection 1 g ceftriaxone is dissolved in 3.5 ml of 1% Lidocaine Hydrochloride solution. The solution should be administered by deep intramuscular injection. Dosages greater than 1 g should be divided and injected at more than one site.

The displacement volume of 1 g of Ceftriaxone is 0.71 ml in water for injections and 1% lidocaine hydrochloride solution. When adding 10 ml of water for injections, the final concentration of the reconstituted solution is 93.37 mg/ml. When adding 3.5 ml of 1% lidocaine hydrochloride solution, the final concentration of the reconstituted solution is 237.53 mg/ml

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Sance Laboratories Private Limited, VI/51B, P.B No.2, Kozhuvanal, Pala, Kottayam- 686573, Kerala, India.

Manufacturing site address:
Sance Laboratories Private Limited, VI/51B, P.B No.2, Kozhuvanal, Pala, Kottayam- 686573, Kerala, India.

8. Marketing authorization number
CTD 9827

9. Date of first registration
19/03/2023

10. Date of revision of the text:
15/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable