CEF-3

Long acting, broad spectrum Cephalosporin for parenteral use

COMPOSITION

Each vial contains:

Ceftriaxone disodium equivalent to Ceftriaxone 250 mg, 500 mg, 1 g.

Each pack for IM Injection consists of a vial with the active ingredient and a 2 -or 3.5 ml ampoule of 1% lidocaine solution.

Each pack for IV Injection consists of a vial with the active ingredient and a 5 -or 10 ml ampoule of water for injection.

PHARMACODYNAMICS

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 lead to bacterial cell lysis and death.

Resistance

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

- Hydrolysis by 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 penumoniae	≤ 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

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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

PHARMACOKINETICS

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 100mg/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.

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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).

INDICATION

Infections caused by pathogens sensitive to CEF-3 e.g., respiratory tract infections, particularly pneumonia, and ear, nose and throat infections; Renal and urinary tract infections; Sepsis; Meningitis; Infection in patients with impaired defense mechanisms; Perioperative prophylaxis of infections; Infections of the bones, joints, soft tissue, skin and wounds; Abdominal infection (peritonitis, infections of biliary and gastro-intestinal tract); Genital infection including gonorrhea.

RECOMMENDED DOSAGE

General

Standard dosage

Adults and children over 12 years

The usual dosage is 1–2 g of CEF-3 *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.

Duration of treatment

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of CEF-3 should be continued for a minimum of 48-72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination treatment

Synergy between CEF-3 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 microorganisms such as *Pseudomonas aeruginosa*. Due to chemical incompatibility between CEF-3 and aminoglycosides, the two drugs must be administered separately at the recommended dosages. Chemical incompatibility with CEF-3 has also been observed with i.v. administration of amsacrine, vancomycin and fluconazole.

Method of administration

As a general rule the solutions should be used immediately after preparation.

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2–8°C). The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The coloration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection. For i.m. injection, CEF-3 250 mg or 500 mg is dissolved in 2 ml, and CEF-3 1 g in 3.5 ml, of 1% lidocaine hydrochloride solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site.

The lidocaine solution should never be administered intravenously.

Intravenous injection. For i.v. injection, CEF-3 250 mg or 500 mg is dissolved in 5 ml, and CEF-3 1 g in 10 ml, sterile water for injections. The intravenous administration should be given over 2–4 minutes.

Intravenous infusion. The infusion should be given over at least 30 minutes. For i.v. infusion, 2 g CEF-3 is dissolved 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%, water for injections. CEF-3 solutions should *not* be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute CEF-3 vials or to further dilute a reconstituted vial for i.v. administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when CEF-3 is mixed with calcium-containing solutions in the same i.v. administration line. CEF-3 must not be administered simultaneously with calcium-containing i.v. solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, CEF-3 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 (i.v. or oral).

Special Dosage Instructions

Pediatric use

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for *once daily* administration:

Neonates (up to 14 days): 20–50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. CEF-3 is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

CEF-3 is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing i.v. solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

For neonates, infants, and children (15 days to 12 years): 20–80 mg/kg once daily.

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

Intravenous doses of ≥ 50 mg/kg bodyweight, in infants and children up to 12 years of age, 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.

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

Geriatric use

No dose adjustment of CEF-3 is required in patients ≥ 65 years of age provided there is no severe renal and hepatic impairment.

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Renal impairment

No dose adjustment is required, provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance <10 ml/min) should the CEF-3 dosage not exceed 2 g daily. Ceftriaxone is not removed by peritoneal- or hemodialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis.

Hepatic impairment

No dose adjustment of CEF-3 is required, provided renal function is not impaired.

Severe renal and hepatic impairment

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

Lyme borreliosis

50 mg/kg to a maximum of 2 g in children and adults, once daily for 14 days.

Gonorrhea (penicillinase-producing and nonpenicillinase-producing strains)

A single i.m. dose of 250 mg.

Perioperative prophylaxis

A single dose of 1-2 g depending on the risk of infection 30-90 minutes prior to surgery. In colorectal surgery, administration of CEF-3 with or without a 5-nitroimidazole, e.g. ornidazole has been proven effective.

CONTRAINDICATIONS

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

History of severe hypersensitivity (e.g., anaphylactic reaction) to any other type of 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) treatment with calcium-containing intravenous solutions including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

*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 intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent.

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

WARNINGS AND PRECAUTIONS

- In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to 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 administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

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) and drug reaction with eosinophilia and systemic symptoms (DRESS)) which can be life-threatening or fatal, have been reported in association with ceftriaxone treatment; however, the frequency of these events is not known.

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.

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 reportedduring 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, a 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.

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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

This medicinal product contains 82mg sodium per 1g vial, equivalent to 4.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Antibacterial spectrum

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

Use of lidocaine

In case a lidocaine solution is used as a solvent**,** ceftriaxone solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information 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.

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.

INTERACTIONS WITH OTHER MEDICAMENTS

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form.

Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line.

Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently, and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone.

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

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

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

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

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

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

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

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

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 breast-fed 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.

SIDE EFFECTS

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

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known** [a]
Infections and infestation		Genital fungal infection	Pseudomembranous colitis [b]	Superinfection [b]
Blood and lymphatic system disorders	Eosinophilia Leucopenia	Granulocytopenia Anaemia		Haemolytic anaemia [b] Agranulocytosis

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	Thrombocytopenia	Coagulopathy		
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity [b] Jarisch-Herxheimer reaction [b]
Nervous system disorders		Headache Dizziness		Encephalopathy [d] Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea [b] Loose stool	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.

b See section Precautions and Warnings

c Usually reversible upon discontinuation of ceftriaxone

d Reversible encephalopathy has been reported with the use of ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.

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.

INSTRUCTION FOR USE

Cef-3® solutions should be used immediately after reconstitution. The reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (25ºC) and for 24 hours in refrigerator (2-8ºC). The appearance colour of solution ranges from yellow to amber depending on the concentration, length of storage and diluent used.

INCOMPATABILITIES

The admixture of ceftriaxone sodium injection with other antibacterials is not recommended. The admixture of beta-lactam antibacterials (penicillins and cephalosporins) and aminoglycosides may result in substantial mutual inactivation. If they are administered concurrently, they should be administered in separate sites. Do not mix them in the same intravenous bag or bottle.

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STORAGE

Store below 30C.

The reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (25°C) and for 24 hours in refrigerator (2-8°C).

SHELF-LIFE

Please refer to the carton label for the expiry date.

DOSAGE FORM AND PACKS

Packs for IM injection containing 1 vial with dry substance equivalent to 250 mg, 500 mg or 1 g. Ceftriaxone and 1 ampoule 2 ml or 3.5 ml of Lidocaine HCl 1 % solution.

Packs for IV injection containing 1 vial with dry substance equivalent to 250 mg, 500 mg or 1 g Ceftriaxone and 1 ampoule 5 ml or 10 ml of Sterile Water for Injection.

Manufactured by:

Siam Bheasach Co., Ltd.
123 Soi Chokechairuammitr, Vibhavadi-Rangsit Road, Chatuchak, Bangkok 10900
and 9 Soi Chokechairuammitr 3, Vibhavadi-Rangsit Road, Dindang, Bangkok 10400, Thailand

Product Registration Holder, Importer:

SPG PHARMA (MALAYSIA) SDN BHD
Suite 1701, Block A, Damansara Intan e-Business Park,

No 1, Jalan SS20/27, 47400 Petaling Jaya,

Selangor Darul Ehsan, Malaysia

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