pharmaniaga®

eriax

POWDER FOR SOLUTION FOR INJECTION OR INFUSION 1G

CEFTRIAXONE(as sodium)

Name of The Medicinal Product

Eriax Powder for Solution for Injection or Infusion 1 g

Qualitative and Quantitative Composition

Each vial contains Ceftriaxone Sodium 1.19 g (equivalent to Ceftriaxone 1 g)

Product Description

White to yellowish-orange crystalline powder

Pharmacodynamics

Mechanism of action

The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis. Ceftriaxone exerts in-vitro activity against a wide range of gram-negative and gram-positive micro-organisms. Ceftriaxone is highly stable to most ß-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following micro-organisms in vitro and in clinical infections.

Gram-positive aerobes

Staphylococcus aureus (methicillin-sensitive), Staphylococci coagulase-negative, *Streptococcus pyogenes* (ß-hemolytic, group A), *Streptococcus agalactiae* (ß-hemolytic, group B), ß-hemolytic Streptococci (non-group A or B), *Streptococcus viridans, Streptococcus pneumoniae*.

Note: methicillin-resistant *Staphylococcus* spp. is resistant to cephalosporins, including ceftriaxone. In general, *Enterococcus* faecalis, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram-negative aerobes

*Acinetobacter lwoffi, Acinetobacter anitratus (*mostly *A. baumanii)*, Aeromonas hydrophila, Alcaligenes faecalis, Alcaligenes odorans, Alcaligenes-like* bacteria*, Borrelia burgdorferi,*
Capnocytophaga spp*., Citrobacter diversus (*including *C. amalonaticus), Citrobacter freundii*,*
Escherichia coli, Enterobacter aerogenes, Enterobacter cloacae*, Enterobacter* spp*. (*other)**,*
*Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae**, Moraxella catarrhalis (*former *Branhamella catarrhalis), Moraxella osloensis, Moraxella* spp. (other*), Morganella morganii, Neisseria gonorrhea, Neisseria meningitidis, Pasteurella multocida, Plesiomonas shigelloides, Proteus mirabilis, Proteus penneri*, Proteus vulgaris*, Pseudomonas fluorescens*, Pseudomonas* spp. (other*)*, Providentia rettgeri*, Providentia* spp. (other)*, Salmonella typhi, Salmonella* spp. (nontyphoid*), Serratia marcescens*, Serratia* spp. (other*)*, Shigella* spp., *Vibrio* spp., *Yersinia enterocolitica, Yersinia spp. (other).*

* Some isolates of these species are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase.

** Some isolates of these species are resistant due to production of extended spectrum, plasmid mediated ß-lactamase.

Note: Many strains of the above micro-organisms that are multiple resistant to other antibiotics e.g. amino-penicillins and ureido-penicillins, older cephalosporins and aminoglycosides, susceptible to ceftriaxone. *Treponema pallidum* is sensitive in vitro and in animal experiments. Clinical investigations indicate that primary and secondary syphilis respond well to ceftriaxone therapy. With a few exceptions clinical P. aeruginosa isolates are resistant to ceftriaxone.

Anaerobic organisms

Bacteroides spp. (bile-sensitive)*, *Clostridium* spp. (excluding *C. difficile), Fusobacterium nucleatum*, *Fusobacterium* spp. (other), *Gaffkia anaerobica* (formerly *Peptococcus*), *Peptostreptococcus* spp.

* Some isolates of these species are resistant to ceftriaxone due to ß-lactamase-production.

Note: Many strains of ß-lactamase-*producing Bacteroides* spp. (notably *B. fragilis*) are resistant. *Clostridium difficile* is resistant.

Susceptibility to ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardized techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued the following interpretative breakpoints for ceftriaxone:

	Susceptible	Moderately Susceptible	Resistant
Dilution test inhibitory concentrations in mg/l	=8	16-32	=64
Diffusion test (disk with 30 µg ceftriaxone), inhibition zone diameter in mm	=21	20-14	=13

Micro-organisms should be tested with the ceftriaxone disk since it has been shown by in-vitro tests to be active against certain strains resistant to cephalosporin class disks.

Where NCCLS recommendations are not in daily use, alternative, well-standardized, susceptibility-interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

Pharmacokinetics

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, 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.

Absorption

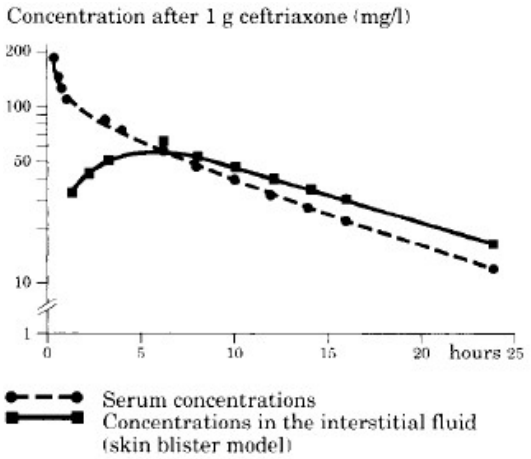
Eriax is administered as an intramuscular injection or as an i.v. injection or infusion. The maximum plasma concentration after a single i.m. dose of 1 g is about 81 mg/l and is reached in 2–3 hours after administration. The area under the plasma concentration-time curve after i.m. administration is equivalent to that after i.v. administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone.

After intravenous bolus administration of ceftriaxone 1 g, mean peak plasma ceftriaxone levels are approximately 200 mg/l. After intravenous infusion of ceftriaxone 1g, the plasma ceftriaxone levels are approximately 150mg/l. 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.
On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours (see figure).



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).

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 metabolised systemically; but is converted to inactive metabolites by the gut flora.

Elimination
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 8 hours.

Pharmacokinetics in Special Populations
Pediatric 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.

Geriatric Population
In elderly persons aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Renal impairment
In patients with renal impairment, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased (less than two-fold), even in patients with severely impaired renal function.

The 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.

Hepatic Impairment
In patients with hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased, (less than two-fold), even in patients with severely impaired renal function.

In this patient population, 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.

Indication
Eriax is indicated for infections caused by pathogens sensitive to Ceftriaxone, e.g.:

- sepsis;
- meningitis;
- disseminated Lyme borreliosis (early and late stages of the disease);
- 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.

And perioperative prophylaxis of infections.

Recommended Dosage

General

Standard dosage

Adults and children over 12 years
The usual dosage is 1–2 g of Eriax 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 Eriax 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 Eriax 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 Eriax and aminoglycosides, the two drugs must be administered separately at the recommended dosages. Chemical incompatibility with Eriax 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 colouration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection. For i.m. injection, Eriax 1g is dissolved in 3.5ml 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, Eriax 1g is dissolved in 10ml, of sterile water for injections. The intravenous administration should be given over 2–4minutes.

Intravenous infusion. The infusion should be given over at least 30 minutes. For i.v. infusion, 2 g Eriax 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. Ceftriaxone 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 Eriax 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 Eriax is mixed with calcium-containing solutions in the same i.v. administration line. Eriax 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, Eriax 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. Eriax is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Eriax 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 Eriax is required in patients ≥ 65 years of age provided there is no severe renal and hepatic impairment.

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

Eriax 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 Eriax 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 Eriax with or without a 5-nitroimidazole, e.g. ornidazole hasbeen proven effective.

Route of Administration
Powder for solution for injection:
- intramuscular injection
- intravenous injection

Powder for solution for infusion:
- intravenous infusion

Contraindications
Hypersensitivity
Eriax 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 agents may be at greater risk of hypersensitivity to ceftriaxone

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

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

Hyperbilirubinemic newborns
Hyperbilirubinemic newborns should not be treated with ceftriaxone. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.

Neonates and calcium-containing i.v. solutions
Eriax 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.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Eriax and calcium containing fluids. In some of these cases, the same intravenous infusion line was used for both Eriax and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

Warnings and Precautions

Hypersensitivity
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 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 hypersensitivity to other beta-lactam agents.

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 discontinued until the etiology is determined.

Clostridium difficile associated diarrhea (CDAD)
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. Toxin hyperproducing 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.

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

Calcium-ceftriaxone precipitates
Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving ceftriaxone, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in pediatric patients. Precipitates disappear after discontinuation of ceftriaxone therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of ceftriaxone treatment should be considered by the physician based on an individual benefit-risk assessment.

In the available scientific data, there are no reports of intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. However, ceftriaxone should not be mixed or administered to any patient simultaneously with calcium-containing solutions, even via different infusion lines.

Pancreatitis
Cases of pancreatitis, possibly of biliary obstruction aetiology, have 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 cofactor role of Ceftriaxone-related biliary precipitation cannot be ruled out.

Pediatrics
Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described under 2.2 Dosage and Administration. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy.

Blood monitoring
During prolonged treatment the complete blood count should be done at regular intervals.

Influence on diagnostic tests
In patients treated with Ceftriaxone the Coombs' test may become falsely positive. Eriax, like other antibiotics, may result in false-positive test results for galactosemia.

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

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.

Interactions with Other Medicaments
No impairment of renal function has so far been observed after concurrent administration of large doses of Ceftriaxone and potent diuretics (e.g. furosemide). 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.

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.

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 i.v. administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Eriax is mixed with calcium-containing solutions in the same i.v. administration line. Eriax 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, Eriax 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.

Pregnancy and Lactation

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed.

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Eriax is administered to a nursing woman.

Undesirable Effects

Adverse drug reactions are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100),
rare (≥1/10,000 to <1/1,000).

Adverse reactions	Frequency category
Blood and lymphatic system disorders	
Eosinophilia	Common
Leucopenia	Common
Thrombocytopenia	Common
Granulocytopenia	Uncommon
Anaemia	Uncommon
Coagulopathy	Uncommon
Gastrointestinal disorders	
Diarrhoea	Common
Loose stools	Common
Nausea	Uncommon
Vomiting	Uncommon
General disorders and administration site conditions	
Phlebitis	Uncommon
Injection site reactions	Uncommon
Pyrexia	Uncommon
Oedema	Rare
Chills	Rare
Hepatobiliary disorders	
Hepatic enzyme increased	Common
Infections and infestations	
Genital fungal infection	Uncommon
Pseudo-membranous colitis	Rare
Investigations	
Blood creatinine increased	Uncommon
Nervous system disorders	
Encephalopathy*	Not known
Headache	Uncommon
Dizziness	Uncommon
Renal and urinary disorders	
Haematuria	Rare
Glycosuria	Rare
Respiratory, thoracic and mediastinal disorders	
Bronchospasm	Rare
Skin and subcutaneous tissue disorders	
Rash	Common
Pruritus	Uncommon
Urticaria	Rare

**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.*

Postmarketing Experience

The following adverse drug reactions have been identified from post-marketing experience with ceftriaxone. These reactions are reported from a population of uncertain

size, therefore, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure.

Systemic side effects

Gastrointestinal complaints: pancreatitis, stomatitis and glossitis.
Hematological changes: isolated cases of agranulocytosis (<500/mm^3) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Skin reactions: acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

Nervous system disorders: convulsion, encephalopathy

Reversible encephalopathy has been reported with the use of cephalosporins, including 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.

Infections and infestations: superinfection

Other, rare side effects: symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

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.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Ceftriaxone 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. At least one fatality has been reported in a neonate in whom Ceftriaxone and calcium containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

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.

Local side effects
In rare cases, phlebitis reactions occurred after i.v. administration. These may be minimized by slow (2–4 minutes) injection. Investigations: Coombs test false positive, galactosemia test false positive, non-enzymatic methods for glucose determination false positive.

Symptoms and Treatment of Overdose

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

Effects on Ability to Drive and Use Machine

During treatment with Eriax, 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.

Special Instruction for Use, Handling and Disposal

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available in your location.

Disposal of syringes/sharps
The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharp container (puncture-proof disposable container).
- Keep this container out of the reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Storage Conditions

Unopened: Store below 30°C.
Keep vial in the outer container.

After reconstitution:

Reconstitution solution	Storage condition	
	30°C	2-8°C
Sterile water for injection [100mg/ml]	Stable within 6 hours	Stable within 24 hours
1% lidocaine [250mg/ml]		
1% lidocaine [350mg/ml]		
Glucose injection (5%) [10mg/ml]		
Glucose injection (10%) [10mg/ml]		
Sodium chloride (0.9%) [10mg/ml]		
0.45% sodium chloride and 2.5% glucose solution [10mg/ml]		
Glucose injection (5%) [50mg/ml]		
Glucose injection (10%) [50mg/ml]		
Sodium chloride (0.9%) [50mg/ml]		
0.45% sodium chloride and 2.5% glucose solution [50mg/ml]		
6% Dextran in 5% Glucose (10mg/ml)		
6% Dextran in 5% Glucose (50mg/ml)		

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

Keep vial in the outer container.

Packaging

1 vial: Preserved in a 10ml transparent and colorless USP Type II glass mould vials, gray butyl rubber stopper, blue aluminium- plastic caps, adhesive label. 1 vial then packed onto outer box.

5 vials: Preserved in a 10ml transparent and colorless USP Type II glass mould vials, gray butyl rubber stopper, blue aluminium- plastic caps, adhesive label. 5 vials then packed onto outer box.

10 vials: Preserved in a 10ml transparent and colorless USP Type II glass mould vials, gray butyl rubber stopper, blue aluminium- plastic caps, adhesive label. 10 vials then packed onto outer box.

Manufacturer

Reyoung Pharmaceutical Co., Ltd.
No. 1, Ruiyang Road, Yiyuan County,
Shandong Province, The People's Republic of China

Product Registration Holder

Pharmaniaga Marketing Sdn Bhd (198401005734)
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