Package Insert

1. NAME OF THE MEDICINAL PRODUCT

CEFTRIAXONE ALVOGEN POWDER FOR SOLUTION FOR INJECTION/ INFUSION 1G/VIAL
CEFTRIAXONE ALVOGEN POWDER FOR SOLUTION FOR INJECTION/ INFUSION 2G/VIAL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g ceftriaxone (as ceftriaxone sodium).
Each vial contains 2 g ceftriaxone (as ceftriaxone sodium).

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

Almost white or yellowish, slightly hygroscopic, crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible micro-organisms (see section 5.1) and when parenteral therapy is required:

- Pneumonia.
- Sepsis.
- Meningitis.
- Bone, skin and soft tissue infections.
- Infections in neutropenic patients.
- Gonorrhoea.
- Peri-operative prophylaxis of infections.

Treatment may be started before the results of susceptibility tests are known.

Consideration should be given to official guidance on the appropriate use of antibacterials.

4.2 Posology and method of administration

Posology
CEFTRIAXONE ALVOGEN may be administered by intramuscular injection, intravenous injection, or as intravenous infusion, after reconstitution of the solution according to the directions given below.

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.

Dose and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition.

Combination therapy

Synergy between ceftriaxone and aminoglycosides has been demonstrated with many gram-negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life threatening infections due to micro-organisms such as Pseudomonas aeruginosa. Because of physical incompatibility the two drugs must be administered separately at the recommended dosages.

Standard dosage

Adults and children over 12 years

The usual dosage is 1-2 g of CEFTRIAXONE ALVOGEN 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.

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

Gonorrhoea (penicillase-producing and nonpenicillinase-producing strains)
A single dose of 250 mg intramuscularly should be administered.

Peri-operative prophylaxis
A single dose of 1-2 g depending on the risk of infection of 30-90 minutes prior to surgery. In colorectal surgery, administration of CEFTRIAXONE ALVOGEN with or without a 5-nitroimidazole, e.g. ornidazole (separate administration, see 2.2 Dosage and Administration) has been proven effective.

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

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. It is not necessary to differentiate between premature and term infants.

For Infants and children (15 days to twelve 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 or more per kg should be given by infusion over at least 30 minutes.

Patients with renal and hepatic impairment
In patients with impaired renal function, there is no need to reduce the dose of CEFTRIAXONE ALVOGEN provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance < 10 ml per minute) should the daily dose not exceed 2 g daily.

In patients with liver damage there is no need for the dose to be reduced provided renal function is intact.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of CEFTRIAXONE ALVOGEN should be determined at regular intervals and dose adjusted.

In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dose adjustments are necessary, since the elimination rate in these patients may be reduced.

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 meningitides 4 days
Haemophilus influenzae 6 days
Streptococcus pneumoniae 7 days

Method of administration
CEFTRIAXONE ALVOGEN is intended for intravenous or intramuscular use.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to beta-lactam antibiotics.

In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life).

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 (see Dosage and administration and Interactions with Calcium-Containing Products).

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.

4.4 Special warnings and precautions for use

As with other cephalosporins, anaphylactic reactions with fatal outcome were also reported, even if a patient is not known to be allergic or previously exposed.

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam antibiotic. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any

other beta-lactam antibiotic (see section 4.3). Ceftriaxone should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam antibiotic.

Ceftriaxone should be given with caution to patients who have other allergic diatheses.
Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic syndroms (DRESS)) which can be life-threatening or fatal, have been reported in association of ceftriaxone treatment; however, the frequency of these events is not known (see section 4.8).

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 reactions occurs.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns 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 newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

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.
In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing i.v. 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 a compatible fluid.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterials, including ceftriaxone, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterials 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterials.

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 with non-susceptible micro-organisms may occur as with other antibacterials.

An immune-mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. Severe cases of haemolytic anaemia, including

fatalities, have been reported during 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.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of ceftriaxone. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

Ceftriaxone should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non- susceptible organisms, such as *enterococci* and *Candida spp.*

In severe renal and hepatic insufficiency, dose should be reduced according to given recommendations (see section 4.2).

Ceftriaxone may precipitate in the gallbladder and then be detectable as shadows on ultrasound (see section 4.8). This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80 mg/kg body weight should be avoided because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

Shadows, which have been mistaken for gallstones are however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended.

Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the medicinal product to produce a positive Coombs' test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

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.

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the doses described under “Dose and administration”. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

During prolonged treatment a complete blood count should be performed at regular intervals.

In case lidocaine is used as a solvent, ceftriaxone solutions should only be used for intramuscular injection.

The stated dose should not be exceeded.

4.5 Interaction with other medicinal products and other forms of interaction

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

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with ceftriaxone.

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. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

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 ceftriaxone is mixed with calcium-containing solutions in the same i.v. administration line. Ceftriaxone 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, 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.

Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

In patients treated with ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine- glucose determination during therapy with ceftriaxone should be done enzymatically.

4.6 Fertility, pregnancy and lactation

Pregnancy
For ceftriaxone, limited clinical data on exposed pregnancies are available. Ceftriaxone crosses the placental barrier. Reproductive studies in animals have shown no evidence of embryotoxicity, foetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed. Safety in human pregnancy is not established.

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

4.7 Effects on ability to drive and use machines

Since ceftriaxone sometimes induces dizziness the ability to drive and use machines can be impaired.

4.8 Undesirable effects

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

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 IV infusion line was used for both ceftriaxone and calcium- containing fluids and in some a precipitate was observed in the IV 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 IV lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

The frequency terms listed are defined as follows:
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), Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

Infections and infestations

Rare: Mycosis of the genital tract.

Superinfections of various sites with yeasts, fungi or other resistant organisms are

possible. Blood and lymphatic system disorders

Rare: Neutropenia, leukopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time.

Very rare (including isolated reports): Positive Coombs' test, coagulation disorders, agranulocytosis (< 500/m^3), mostly after 10 days of treatment and following total doses of 20 g ceftriaxone and more.

Immune system disorders

Rare: Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

Not known: Jarisch-Herxheimer reaction (see section 4.4)

Nervous system disorders

Rare: Headache, dizziness.

Gastrointestinal disorders

Common: Loose stools or diarrhoea, nausea, vomiting.

Rare: Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.

Very rare (including isolated reports): Pseudomembranous colitis (mostly caused by *Clostridium difficile*), pancreatitis (possibly caused by obstruction of bile ducts). Therefore, the possibility of the disease should be considered in patients who present with diarrhoea following use of antibacterials.

Hepatobiliary disorders

Rare: Increase in serum liver enzymes (AST, ALT, alkaline phosphatase).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed (see section 4.4), mostly 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, in some studies to above 30%. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Skin and subcutaneous tissue disorders

Uncommon: Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritus, oedema.

Very rare (including isolated reports): Erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome/toxic epidermal necrolysis.

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Renal and urinary disorders

Rare: Increase in serum creatinine, oliguria, glycosuria, haematuria.

Very rare (including isolated reports): Renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (80 mg/kg/day and more) or total doses exceeding 10 g and with other risk factors such as dehydration or immobilisation. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

General disorders and administration site conditions

Rare: Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine solution is painful.

Postmarketing Experience

Nervous system disorders: 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.

4.9 Overdose

In the case of overdose nausea, vomiting, diarrhoea, can occur. Ceftriaxone concentration can not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 (see 2. Clinical Particulars):

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 gonorrhoea, 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. (non- typhoid), *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, are 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.

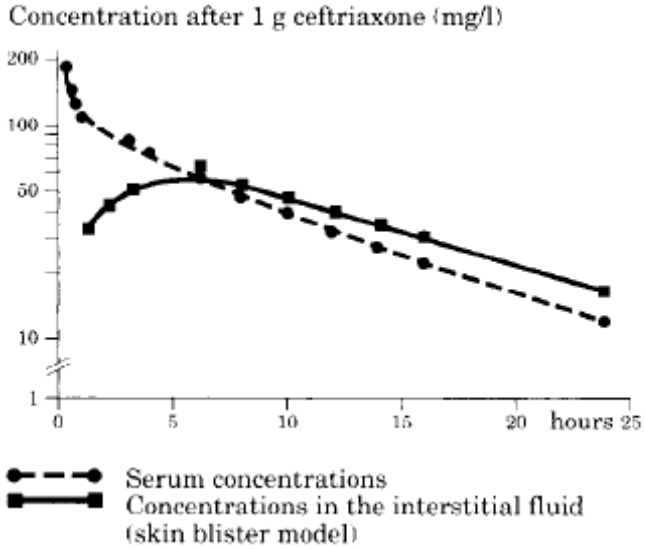
5.2 Pharmacokinetic properties

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.

Absorption
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

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, and the binding decreases with the increase in concentration, e.g. from 95% binding at plasma concentrations of <100 mg/l to 85% binding at 300 mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Penetration into particular tissues

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children: Ceftriaxone concentrations exceed 1.4 mg/l in the Cerebrospinal Fluid (CSF) 24 hours after i.v. injection of Rocephin in doses of 50-100 mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after i.v. injection and gives an average value of 18 mg/l. Mean CSF levels are 17% of plasma concentrations in patients with bacterial meningitis and 4% in patients with aseptic meningitis.

In adult meningitis patients, administration of 50 mg/kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common meningitis pathogens.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Metabolism

Ceftriaxone is not metabolized 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

Patients with renal impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone

is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Patients with hepatic impairment
Refer to “Patients with renal impairment” above.

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

Children
In neonates, urinary recovery accounts for about 70% of the dose. In infants aged less than 8 days the average elimination half-life is usually two to three times that of young adults.

5.3 Preclinical safety data

Teratogenicity
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents. In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for i.v. administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions (see section 4.2, 4.3, 4.4 and 4.8). Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

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

6.3 Shelf life

Shelf life prior to reconstitution:
As indicated on the outer packaging.

Shelf life of the reconstituted product:
Following reconstitution chemical and physical in-use stability has been demonstrated for 24 to 36 hours at 25°C or 10 days at 2-8°C. The vials must be kept in the outer carton to protect from light.

6.4 Special precautions for storage

As indicated on the outer packaging.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Vial containing 1 g ceftriaxone: 15 ml or 30 ml type I glass vial closed by bromobutyl rubber stopper and sealed by aluminum flip-off cap.

Vial containing 2 g ceftriaxone: 30 ml type I glass vial closed by bromobutyl rubber stopper and sealed by aluminum flip-off cap.

Pack size: 50 vials per carton box

6.6 Special precautions for disposal and other handling

The use of freshly prepared solutions is recommended. These maintain potency for 24 to 36 hours at 25°C or 10 days at 2-8°C. Protect from light.

Reconstitution table

Route of administration	***Diluents***	***Storage container***	***Period***	
			Room temperature 25°C	*Refrigerator 5°C ± 3°C*
Intramuscular injection	Water for injection	Glass bottle and PP bottle	36 hours	10 days
Intravenous injection	Water for injection	Glass bottle and PP bottle	36 hours	10 days
Intravenous infusion	Sodium chloride 9 mg/ml (0.9%) solution for injection	Glass bottle and PP bottle	36 hours	10 days
	5% glucose solution	Glass bottle and PP bottle	36 hours	10 days
	10% glucose solution	Glass bottle	36 hours	10 days
		PP bottle	24 hours	10 days

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

7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
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8. DATE OF REVISION OF THE TEXT

03/2021