PACKAGE INSERT TEMPLATE FOR CEFTRIAXONE POWDER FOR SOLUTION FOR INJECTION /INFUSION

Brand or Product Name
[Product name] Powder for Solution For Injection/ Infusion 1g

Name and Strength of Active Substance(s)
Ceftriaxone sodium…mg equivalent to 1g Ceftriaxone

Product Description
[Visual description of the appearance of the product (eg colour, odour etc)
eg White to off-white caked powder. Upon reconstitution, ceftriaxone powder yields a pale yellow to amber *solution]*

Pharmacodynamics

Ceftriaxone is a 2-aminothiazolyl methoxyimino third-generation cephalosporin derivative. Ceftriaxone offers good activity against gram-negative organisms with reasonable activity against gram-positive organisms.

Ceftriaxone, a bactericidal antimicrobial, inhibits bacterial wall synthesis of actively dividing cells by binding to one or more penicillin bind proteins (PBPs). These proteins are associated with the bacterial cell membrane and probably serve as synthesis. The result is formation of a defective cell wall that is osmotically unstable. Bacterial species have a unique set of PBPs. The affinity pattern of ceftriaxone for the PBPs for different bacterial species affects the drug's antimicrobial spectrum of activity. It is also felt that cephalosporins, as well as penicillins, may increase the breakdown of the cell wall of bacteria by decreasing the availability of an inhibitor of murein hydrolase, an enzyme involved in cell division. If unimposed, this enzyme can destroy the integrity of the cell wall.

In the presence of beta-lactamase bacteria, including penicillinases and cephalosporinases, ceftriaxone maintains a high degree of stability.

It is active against most of the following microorganism strains

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, lebsiella 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.

Pharmacokinetics
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
Mean peak plasma concentrations of about 40 and 80 micrograms/mL have been reported 2 hours after intramuscular injection of 500 mg and 1 g of ceftriaxone respectively.
The bioavailability of intramuscularly administered ceftriaxone is 100%.

Distribution
The volume of distribution of ceftriaxone is 7-12 L.

It is widely distributed in body tissues and fluids.
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. It crosses both inflamed and non-inflamed meninges, generally achieving therapeutic concentrations in the CSF. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations occur in bile.

Protein binding: Ceftriaxone has nonlinear dose-dependent pharmacokinetics because of its protein binding; about 85 to 95% is bound to plasma proteins depending on the concentration of ceftriaxone.

Metabolism
Ceftriaxone is minimally metabolized. The drug is converted to inactive metabolites by the gut flora.

Excretion

Total plasma clearance is 10-22 ml/min.

About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found in the faeces as unchanged drug and microbiologically inactive compounds.

The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 and 9 hours; it may be prolonged in neonates. The half-life does not change appreciably in patients with moderate renal impairment, but it may be prolonged in severe impairment especially when there is also hepatic impairment.

Ceftriaxone is not dialyzable.

Pharmacokinetics in Special Populations

Patients with renal impairment

Prolonged half-life in severe or end-stage renal disease.

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

In many patients no alteration in dosage is necessary, but some individuals have reduced non-renal clearance despite apparently normal hepatic function. It is advisable to monitor plasma ceftriaxone in patients with severe renal impairment and unknown non-renal clearance.

Patients with hepatic impairment

Minimal alterations in the pharmacokinetics of ceftriaxone were observed in patients with hepatic impairment compared to healthy adult subjects.

Elderly

In elderly persons aged over 75 years the average elimination half-life is usually two to three times that of young adults. The average elimination half-life of ceftriaxone in elderly patients (mean age 70.5 years) was increased.

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.

Clearance of the drug in children is 55 mL/kg/hr compared to adults which is 18 mL/kg/hr.

Indication

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 gonorrhoea.

And perioperative prophylaxis of infections.

Recommended Dosage

Standard dosage

Adults and children over 12 years

The usual dosage is 1-2 g of ceftriaxone *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 therapy

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

Combination therapy

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

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 ℃).

*Depending on the product formulation, the colour of ceftriaxone solution may be different after reconstitution.

Intramuscular injection.

For i.m. injection, ceftriaxone 250 mg or 500 mg is dissolved in 2ml, and ceftriaxone 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, ceftriaxone 250 mg or 500 mg is dissolved in 5 ml, and ceftriaxone 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 ceftriaxone 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%, hydroxy ethyl starch 6-10%, 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 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.
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

Patients with hepatic impairment
In patients with *liver damage*, there is no need for the dosage to be reduced *provided renal function is not impaired*.

Patients with renal impairment
In patients with *impaired renal function*, there is no need to reduce the dosage of ceftriaxone *provided hepatic function is not impaired*. Only in cases of preterminal renal failure (creatinine clearance <10 ml/min) should the ceftriaxone dosage not exceed 2 g daily.

In *patients with both severe renal and hepatic dysfunction*, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary the dose should be adjusted.

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

Elderly
The dosages recommended for adults require no modification in geriatric patients.

Children
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.

Ceftriaxone 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 should be given by infusion over at least 30 minutes.

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

Haemophilus influenzae 6 days
Streptococcus pneumoniae 7 days

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

Gonorrhoea (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 of 30-90 minutes prior to surgery. In colorectal surgery, administration of ceftriaxone with or without a 5- nitroimidazole, e.g. ornidazole has been proven effective.

Contraindications

- Ceftriaxone is contraindicated in neonates (≤28 days of age) 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.
- Hypersensitivity to cephalosporin antibiotics.
- Hypersensitivity to penicillin may also be allergic to ceftriaxone
- Hyperbilirubinaemic neonates. Treatment with ceftriaxone may increase risk of bilirubin encephalopathy (kernicterus), especially in premature neonates.

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.

Anaphylactic reactions with fatal outcome were also reported, even if a patient is not known to be allergic or previously exposed. History of drug allergy may increase risk of acute hypersensitivity reaction.

Hypersensitivity to penicillins.

Hemolytic anemia, including fatal cases, has been reported; discontinue therapy if hemolytic anemia occurs.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of 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* causes 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.

Prolonged treatment may result in overgrowth of nonsusceptible organisms (superinfection).

Sonographic abnormalities in gallbladder: ceftriaxone-calcium salt precipitate may be misinterpreted as gallstones.

Biliary stasis and biliary sludge risk factors (preceding major therapy, severe illness, total parenteral nutrition); Increased risk of pancreatitis, possibly secondary to biliary obstruction.

Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Hepatic dysfunction with significant renal disease: increased risk of drug toxicity.

Malnutrition : increased risk of altered prothrombin time due to low vitamin K stores.

Renal failure: increased risk of drug toxicity.

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

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

Local reactions (eg phlebitis) may be minimized by slow (2-4 minutes) injection. Intramuscular injection *without* lidocaine solution is painful.

Effects on the ability to drive and use machines
There are no data to indicate any effect on a person's ability to drive or use machines.

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 no evidence that ceftriaxone increases renal toxicity of aminoglycosides.

Ceftriaxone has an N-methylthiotriazine side-chain and may have the potential to increase the effects of anticoagulants and to cause a disulfiram-like reaction with alcohol.

The renal excretion of ceftriaxone is not affected by probenecid.

Concurrent use of ceftriaxone and the following may result in formation of ceftriaxone-calcium precipitates and is contraindicated in neonates:

- Calcium Acetate
- Calcium Chloride
- Calcium Gluceptate
- Calcium Gluconate
- Ringer's Solution
- Lactated Ringer's Solution

Concurrent use of ceftriaxone and cyclosporine may result in an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias).

Concurrent use of ceftriaxone and live typhoid vaccine may result in a decreased immunological response to the typhoid vaccine.

Concurrent use of ceftriaxone and warfarin may result in an increased risk of bleeding.

Statement on Usage During Pregnancy and Lactation

Pregnancy

There are no well-controlled studies of ceftriaxone use in pregnant women. The effects, if any, on the developing fetus are unknown. Cephalosporins, in general, are considered safe for use in pregnancy. A causal relationship between cephalosporins and teratogenic effects has not been found.

Lactation

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

Adverse Effects / Undesirable Effects

Hematologic: Eosinophilia , thrombocytosis , hemolytic anemia leukopenia, granulocytopenia, agranulocytosis

Dermatologic: Induration at injection site, warmth, tightness, or induration ,erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis exanthema, allergic dermatitis, pruritus, urticaria, edema.

Gastrointestinal: Pseudomembranous enterocolitis, biliary sludge or pseudolithiasis, vomiting, dysgeusia, stomatitis and glossitis.diarrhea,nausea,

Immunologic: anaphylactic or anaphylactoid reactions.

Neurologic: Kernicterus of newborn, headache and dizziness,

Renal: Renal failure, serum creatinine raised, serum blood urea nitrogen raised, oliguria

Respiratory: Injury of lung

Reproductive: Vaginitis, candidiasis,, genital mycosis,

Hepatic: Alkaline phosphatase raised, hyperbilirubinemia, liver function tests abnormal

Other, rare side effects: symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, fever, shivering

Laboratory Abnormalities

Influence on diagnostic tests

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

Overdose and Treatment

Symptoms

For cute ingestion of large doses of ceftriaxone: nausea, vomiting, diarrhea, and abdominal pain. Seizures have developed after parenteral overdose.

Treatment

There is no specific antidote.

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. Treatment of overdosage should be symptomatic and supportive.

Incompatibilities

[To add appropriate information based on formulation]

Instructions for Use

[To add appropriate information and graphic]

Storage Conditions

[Store below …. ℃]

Dosage Forms and Packaging Available

[Packaging type & pack size eg 10 ml type I clear glass vial, capped with a butyl rubber stopper/box]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]