

Prontoxone Injection

(Ceftriaxone Sodium)

COMPOSITION

Each vial of 250mg contains:

Sterile Powder of Ceftriaxone Sodium USP eq to Ceftriaxone ... 250mg

Each vial of 500mg contains:

Sterile Powder of Ceftriaxone Sodium USP eq to Ceftriaxone ... 500mg

Each vial of 1 g contains:

Sterile Powder of Ceftriaxone Sodium USP eq to Ceftriaxone 1g

DESCRIPTION

Ceftriaxone sodium is a semi-synthetic 3rd generation cephalosporin antibiotic, with a high degree of stability to β-Lactamases, broad-spectrum activity, effectiveness and convenience of long action.

PHARMACOLOGY

Pharmacodynamics 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 β-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria.

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 IM dose of 1g is about 81mg/l and is reached in 2-3 hours after administration. The area under the plasma concentration-time curve after IM administration is equivalent to that after IV. administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone.

Distribution

Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2g, 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 fluids, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.

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 <100mg/l to 85% binding at 300mg/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 into the inflamed meninges of neonates, infants and children. Ceftriaxone concentrations exceed 1.4 mg/l in the CSF 24 hours after IV injection of Ceftriaxone in doses of 50-100mg/kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after IV injection and gives an average value of 18mg/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 10-22ml/min. Renal clearance is 5-12ml/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.

INDICATIONS AND USAGE

Lower Respiratory Tract Infections caused by Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis or Serratia marcescens.

Acute Bacterial Otitis Media caused by Streptococcus pneumoniae, Haemophilus influenzae (including β-lactamase producing strains) or Moraxella catarrhalis (including g-lactamase producing strains)

Skin and skin Structure infections caused by Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Viridans group streptococci, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis or Peptostreptococcus species.

Urinary Tract Infections (complicated and uncomplicated) caused by Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii or Klebsiella pneumoniae.

Uncomplicated Gonorrhoea (cervical/urethral and rectal) caused by Neisseria gonorrhoeae, including both penicillinase and non-penicillinase producing Strains, and pharyngeal gonorrhoea caused by non-penicillinase producing strains of Neisseria gonorrhoeae.

Bacterial Septicemia caused by Staphylococcus aureus, Streptococcus pneumoniae Escherichia coli, Haemophilus influenzae or Klebsiella pneumoniae.

Bone and Joint Infections caused by Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae or Enterobacter species

Intra-abdominal Infections caused by Echerichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium species (Note: most strains of Clostridium difficile are resistant) or Peptostreptococcus species.

Meningitis caused by Haemophilus influenzae, Neisseria meningitidis or Streptococcus pneumoniae, Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infection caused by Staphylococcus epidermidis and Escherichia coli

Surgical Prophylaxis for preoperative use (surgical prophylaxis) a single dose of 1g administered intravenously 1/2 to 2 hours before surgery is recommended.

Note: Methicillin-resistant staphylococci are resistant to cephalosporin including Ceftriaxone. Most strains of Group D streptococci and enterococci, eg, Enterococcus, (Streptococcus) faecalis, are resistant.

DOSEAGE AND ADMINISTRATION:

Administration

Ceftriaxone may be administered intravenously or intramuscularly

General Instructions

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of Ceftriaxone calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a "Y-site". However, in patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid There have been no reports of an interaction between Ceftriaxone and oral calcium-containing products or interaction between intramuscular Ceftriaxone and calcium-containing products (IV or oral).

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 color from pale yellow to amber, depending on the concentration and length of storage. The coloration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intravenous Injection

For I.V. injection, Ceftriaxone 250mg or 500mg is dissolved in 5ml, and Ceftriaxone 1g in 10ml sterile water for injection. The intravenous administration should be given over 2-4 minutes.

Intravenous Infusion

The infusion should be given over at least 30 minutes. For IV infusion, 2g Ceftriaxone is dissolved in 40ml 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%, hydroxyethyl starch 6-10%, water for injection. Ceftriaxone solutions should not be mixed with or piggy-backed into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Dosage

Ceftriaxone may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution according to the directions given below Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Under most circumstances a once-daily dose or, in the specified indications, a single dose will give satisfactory therapeutic results.

Standard dosage

Standard therapeutic dosage for adults and children (12 years and over) is 1 g once daily. In severe cases or in infections caused by moderately sensitive organisms the dosage may be raised to 4g, once daily.

Duration of therapy

The duration of therapy varies according to the course of 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

In severe, life-threatening infections, the combination of Ceftriaxone sodium with aminoglycosides is indicated without awaiting the results of sensitivity tests. Because of physical incompatibility the two drugs must

be administered separately, not mixed in one syringe / infections with Pseudomonas aeruginosa may require concomitant treatment.

Special dosage instructions

Patients with Renal Impairment

In patients with impaired renal function, there is no need to reduce the dosage of Ceftriaxone provided liver function is intact only in cases of pre-terminal renal failure (creatinine clearance <10ml per minute) should the daily dosage be limited to 2g or less. In severe renal impairment, accompanied by hepatic insufficiency, the plasma concentration of Ceftriaxone should be determined at regular intervals and dosage adjusted. In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

Patients with Hepatic Impairment

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

Elderly

These dosages do not require modification in elderly patients provided that renal and hepatic function is satisfactory.

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for once daily administration;

Neonates (up to 14 days)

A daily dose of 20-50mg/kg body weight, not to exceed 50 mg/kg.

Infants and children (15 days to 12 years)

Standard therapeutic dosage: 20 - 80mg/kg body weight once daily. For children with body weights of 50kg or more the usual adult dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes.

Acute, uncomplicated gonorrhoea

A single dose of 250mg intramuscularly should be administered.

Pre-operative prophylaxis

A single dose of 1-2g depending on the risk of infection of 30-90 minutes prior to surgery. In colorectal surgery, 2g should be given intramuscularly (dosages greater than 1g should be divided and injected at more than one site), or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Use in special populations

Pregnancy

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

Nursing Mothers

Low concentrations of Ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman or as directed by the physician.

CONTRAINDICATIONS:

Ceftriaxone is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS AND PRECAUTIONS:

As with other cephalosporin, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Ceftriaxone. Therefore it is important to consider this diagnosis in patients who present with diarrhoea sub-sequent to the administration of antibacterial agents. Super infections with non-susceptible micro-organisms may occur as with other antibacterial agents. Shadow, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder usually following doses higher than the standard recommended dose. These shadows 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 non-surgical management is recommended. Discontinuation of Ceftriaxone treatment in symptomatic cases should be at the discretion of the physician. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Calcium-containing solutions or products must not be administered within 48 hrs of last administration of Ceftriaxone. Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in neonates and premature has been described. In some cases the infusion lines of administration of Ceftriaxone and calcium containing solutions differed. Cases of pancreatitis possibly of biliary obstruction etiology have been rarely reported in patients treated with Ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge e.g. proceeding 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 dosages described under dosage and administration. Studies have shown that Ceftriaxone, like some other cephalosporin can displace bilirubin from serum albumin. Therefore caution should be exercised

when considering Ceftriaxone treatment in hyperbilirubinemic neonates. Ceftriaxone should not be used in neonates (especially premature) at risk of developing bilirubin encephalopathy. During prolonged treatment the blood should be checked at regular intervals. As with other cephalosporin, anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed.

OVERDOSAGE

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

EXPIRY

See expiry on the pack.

PRESENTATION

Prontoxone 250mg IV injection

Contains a vial with dry substance equivalent to 250mg Ceftriaxone sodium and 1 ampoule of 5ml sterile water for injection.

Prontoxone 500mg IV injections

Contains a vial with dry substance equivalent to 500mg Ceftriaxone sodium and 1 ampoule of 5ml sterile water for injection.

Prontoxone 1g IV injection

Contains a vial with dry substance equivalent to 1 g Ceftriaxone sodium and 2 ampoules of 5ml sterile water for injection.

INSTRUCTIONS

To be sold on prescription of a registered medical practitioner only.

Keep out of reach of children.

Avoid exposure to heat, light and humidity.

Store at 25°C or below.

Improper storage may deteriorate the medicine.

پرنٹو زون

(سینف ٹرائی ایجنڈون)

انجیکشن آئی۔وی۔

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ پر دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 25°C سے کم درجہ حرارت پر رکھی اور روشنی سے محفوظ رکھیں۔

حلول تیار کرنے کے فوراً بعد استعمال کریں۔

صرف وریدی استعمال کیئے

Manufactured by: Friends Pharma (Pvt.) Ltd, 31-KM, Ferozepur Road, Lahore - Pakistan

 **Chiesi**

For

CHIESI PHARMACEUTICALS (PVT.) LTD.

60/1A - XX, Phase III, Commercial Zone,

Khayaban-e-Iqbal, D.H.A. Lahore-Pakistan.