Size : 146 x 278 mm

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CEFTATIME

(Ceftriaxone for Injection USP)

1. NAME OF MEDICINAL PRODUCT

CEFTATIME-500 (Ceftriaxone for Injection USP)

CEFTATIME-1000 (Ceftriaxone for Injection USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFTATIME-500: Each vial contains Ceftriaxone Sodium USP (Sterile) equivalent to Ceftriaxone 500mg.

CEFTATIME-1000: Each vial contains Ceftriaxone Sodium USP (Sterile) equivalent to Ceftriaxone 1000mg.

3. PHARMACEUTICAL FORMS

Dry Powder for Injection (White to yellowish orange crystalline powder)

***Not all presentations are available in every country.**

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 and when parenteral therapy is required:

Septicaemia, Pneumonia, Meningitis, Bone, skin and soft tissue infections, infections in neutropenic patients, Gonorrhoea, Peri-operative prophylaxis of infections associated with surgery.

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

4.2 Dosage and Administration

Ceftriaxone may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution. Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used 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. Therefore, Ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

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.

Adults and children 12 years and over

Standard therapeutic dosage: 1 g once daily.

Severe infections: 2 - 4g daily, normally as a single dose every 24 hours.

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 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Acute, uncomplicated gonorrhoea: A single dose of 250 mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis: Usually 1 g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intramuscularly (dosages greater than 1 g should be divided and injected at more than one site), or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

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: A daily dose of 20 - 50mg/kg body weight, not to exceed 50mg/kg. In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.

Infants and children of up to 12 years

Standard therapeutic dosage: 20 - 50mg/kg body weight once daily.

In severe infections up to 80mg/kg body weight daily may be given. 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. Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

Renal and hepatic 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 patients with liver damage there is no need for the dosage to be reduced provided renal function is intact.

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.

Mode of Administration: For Intravenous (IV) & Intramuscular (IM) use

Product Name	For I.V. administration	For I.M. administration
CEFTATIME-500	Dissolve the contents in 4.8 ml of Sterilized Water for Injections.	Dissolve the contents in 1.8 ml of Sterilized Water for Injections.
CEFTATIME-1000	Dissolve the contents in 9.6 ml of Sterilized Water for Injections.	Dissolve the contents in 3.6 ml of Sterilized Water for Injections.

The reconstituted solution should be used immediately after preparation. Do not use if reconstituted solution is not clear or has suspended matter.

4.3 Contraindications

Ceftriaxone is contraindicated in patients with known hypersensitivity 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).

Full-term newborns (up to 28 days of age)

- With jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired.
- If they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium.

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 drug. 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 drug. 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 drug.

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. In patients of any age Ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Ceftriaxone, and may range in severity from mild diarrhoea to fatal colitis. 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 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 with non-susceptible micro-organisms may occur as with other antibacterial agents.

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone. 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, dosage should be reduced according to given recommendations.

Ceftriaxone may precipitate in the gallbladder and then be detectable as shadows on ultrasound. 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 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates. As the condition appears to be transient and reversible upon discontinuation, therapeutic procedures are not normally indicated.

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.

4.5 Interactions with other medicinal products and other form of interaction

Ceftriaxone has an N-methylthiotriazine ring rather than an N-methylthiotetrazole side-chain, hence it might have potential to cause hypoprothrombinaemia i.e. to increase the effect of anticoagulants and to cause a Disulfiram-like reaction with alcohol.

Unlike many cephalosporins, Probenecid does not affect the renal excretion of Ceftriaxone.

Concurrent administration of large doses of Ceftriaxone and potent diuretics (e.g. furosemide) does not cause any renal function impairment.

Ceftriaxone during simultaneous administration with Aminoglycosides does not cause interference with its action or increase in nephrotoxicity.

In patients treated with Ceftriaxone, the Coombs' test may rarely become false- positive, galactosaemia shows false-positive, hence, urine-glucose determination during therapy with Ceftriaxone should be done enzymatically.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

4.6 Pregnancy and Lactation

Use in Pregnancy

Pregnancy Category B: No adequate and well-controlled studies available and hence Ceftriaxone should not be used unless absolutely indicated.

Use in Lactation

Low concentrations of Ceftriaxone are excreted in the human milk and hence caution should be exercised when Ceftriaxone is administered to the nursing mother.

4.7 Effect on ability to drive and use machines

Since Ceftriaxone sometimes induces dizziness, it may have an effect on ability to drive and use machines.

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.

4.9 Overdosage

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Cephalosporins & related substances, J01DA13

Ceftriaxone has bactericidal activity resulting from the inhibition of bacterial cell wall synthesis ultimately leading to cell death. Ceftriaxone is stable to a broad range of bacterial β-lactamases and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

5.2 Pharmacokinetics Properties

The pharmacokinetics of Ceftriaxone are largely determined by its concentration-dependent binding to serum albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentrations of 300mg/l. Owing to the lower albumin content, the proportion of free Ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Plasma concentrations: Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg Ceftriaxone in 1.06% Lidocaine produces mean peak plasma concentrations of 40 - 70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%.

Excretion: Ceftriaxone is eliminated mainly as unchanged Ceftriaxone, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-life in adults is about 8 hours. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.

5.3 Pre-Clinical Safety Data

No additional data available.

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 IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions. Based on literature reports, Ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides and labetalol.

6.3 ShelfLife

Dry Powder: 24 months from the date of manufacture.

For shelf life of reconstituted product, see section 6.4

6.4 Special Precautions for Storage

Storage prior to reconstitution: Store below 30°C. Protect from light.

Storage after reconstitution: Store the reconstituted solution for not more than 24 hours at 2-8°C or 6 hours at 25°C. Do not freeze.

Keep all medicines out of the reach of children.

6.5 Nature and Contents of Container

CEFTATIME-500: 7.5 ml glass vial USP type III with bromobutylated rubber stopper & Aluminium flip off seal caps, containing a sterile white to yellowish orange crystalline powder. One such vial is packed in a unit carton.

CEFTATIME-1000: 10 ml glass vial USP type III with bromobutylated rubber stopper & Aluminium flip off seal caps, containing a sterile white to yellowish orange crystalline powder. One such vial is packed in a unit carton.

6.6 Special Precautions for Disposal

No special requirements.

7. DATE OF REVISION OF TEXT

March' 2016

Mankind

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