SUMMARY OF PRODUCT CHARACTERISTICS

Emceph Injection

[Ceftriaxone for Injection USP 1 gm]

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1. NAME OF THE MEDICINAL PRODUCT

Emceph Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Emceph Injection

Each vial contains:

Sterile Ceftriaxone Sodium USP

Equivalent to Ceftriaxone ….. 1.0 gm

Each ampoule contains sterile water for Injection USP….10 ml

C-Tri 500

Each vial contains:

Sterile Ceftriaxone sodium USP

Equivalent to Ceftriaxone 500 mg

Each ampoule contains sterile water for Injection USP….5 ml

C-Tri 250

Each vial contains:

Sterile Ceftriaxone sodium USP

Equivalent to Ceftriaxone 250 mg

Each ampoule contains sterile water for Injection USP….5 ml

3. PHARMACEUTICAL FORM

Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lower respiratory tract infections

Skin and skin structure infections

Urinary tract infections

Uncomplicated gonorrhea

Pelvic inflammatory disease

Bacterial speticemia

Bone and joint infections

Meningitis

Surgical prophylaxis

4.2 Posology and method of administration

Ceftriaxone may be administered by deep intramuscular injection or as a slow intravenous injection after reconstitution of the solution according to the directions given below. The dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition.

Intramuscular injection: 1g ceftriaxone should be dissolved in 3.5ml of 1% Lignocaine Hydrochloride Injection BP. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.

Intravenous injection: 1g ceftriaxone should be dissolved in 10ml of Water for Injections BP. The injection should be administered over at least 2-4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Adults and children 12 years and over:

Standard therapeutic dosage: 1g once daily.

Severe infections: 2-4 g daily, normally as a once daily dose.

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: One dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis: Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided

doses at different injection sites), by slow intravenous injection or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Children under 12 years

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

Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual 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.

4.3 Contraindications

Solutions in lignocaine should not be administered intravenously.

Ceftriaxone should not be given to patients with a history of hypersensitivity to cephalosporin antibiotics.

Ceftriaxone should not be given to neonates with jaundice or those who are hypoalbuminaemic or acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired.

4.4 Special warnings and precautions for use

The stated dosage should not be exceeded.

Care is required when administering ceftriaxone to patients who have previously shown hypersensitivity (especially anaphylactic reaction) to penicillins or other non-cephalosporin β-lactam antibiotics, as occasional instances of cross allergenicity between cephalosporins and these antibiotics have been recorded. Anaphylactic shock requires immediate counter measures.

Ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should therefore not be used in jaundiced newborns or in babies who are

hypoalbuminaemic, acidotic or born prematurely, in whom bilirubin binding is likely to be impaired.

Ceftriaxone may precipitate in the gall bladder 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. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone, and conservative management of ceftriaxone precipitate in the gallbladder is recommended.

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

During treatment, the blood count should be checked regularly.

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 can not be ruled out.

Each gram of ceftriaxone sodium contains approximately 3.6mmol sodium.

4.5 Interaction with other medicinal products and other forms of Interaction

No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.

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

The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent, which has been associated with a disulfiram-like effect, when alcohol is taken during therapy with certain cephalosporins.

In an in vitro study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.
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 Pregnancy and Lactation

Pregnancy Category B. Ceftriaxone has not been associated with adverse events on foetal development in laboratory animals but its safety in human pregnancy has not been established. Therefore it should not be used in pregnancy unless absolutely indicated.
Only minimal amounts of ceftriaxone are excreted in breast milk. However, caution is advised in nursing mothers.

4.7 Effects on ability to drive and use machines

No studies to assess the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

The most common side-effects are gastrointestinal, consisting mainly of loose stools and diarrhoea or, occasionally, nausea and vomiting, stomatitis and glossitis. Cutaneous reactions, including maculopapular rash or exanthema, pruritus, urticaria, oedema and allergic dermatitis have occurred. Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome and Lyell's Syndrome/toxic epidermal necrolysis) have been reported.
Haematological reactions have included anaemia (all grades), haemolytic anaemia, leucopenia, neutropenia, thrombocytopenia, eosinophilia, agranulocytosis and positive

Coombs' test. Regular blood counts should be carried out during treatment. Ceftriaxone has rarely been associated with prolongation of prothrombin time.

Headache and dizziness, drug fever, shivering and transient elevations in liver function tests have been reported in a few cases. Other rarely observed adverse reactions include glycosuria, oliguria, haematuria, increase in serum creatinine, mycosis of the genital tract and anaphylactic-type reactions such as bronchospasm.

Very rarely, reversible symptomatic urinary precipitates of calcium ceftriaxone have occurred after ceftriaxone administration. Patients who are very young, immobilised or who are dehydrated are at increased risk. There have been a few reports of anuria and renal impairment following this reaction.

Superinfections with yeasts, fungi or other resistant organisms may occur. A rare side-effect is pseudomembranous colitis which has resulted from infection with Clostridium difficile during treatment with ceftriaxone. Therefore it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Pain or discomfort may be experienced at the site of intramuscular injection immediately after administration but is usually well tolerated and transient. Local phlebitis has occurred rarely following intravenous administration but can be minimised by slow injection over at least 2-4 minutes.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Ceftriaxone is a 2-aminothiazolyl methoxyimino third-generation cephalosporin derivative. Ceftriaxone has potent bactericidal activity against a wide range of Gram-positive and, especially, Gram-negative organisms. The spectrum of activity includes both aerobic and some anaerobic species. It has considerable resistance to degradation by most bacterial β-lactamases.

Microbiology: Ceftriaxone is usually active against the following micro-organisms in vitro and in clinical infections. The list is not exhaustive and focuses on those organisms of particular clinical interest.
Gram-positive aerobes:Staphylococcus aureus (including penicillinase-producing strains) Streptococcus pneumoniae, Streptococcus group A (Streptococcus pyogenes), Streptococcus group B (Streptococcus agalactiae), Streptococcus viridans and Streptococcus bovis.

Note: Methicillin-resistant Staphylococcus spp. are resistant to cephalosporins, including ceftriaxone. Most strains of enterococci (e.g. Enterococcus faecalis) are resistant. Listeria monocytogenes is also not susceptible to ceftriaxone.

Clinical experience

Clinical cure was achieved in 92% of serious bacterial infections with ceftriaxone 1 to 2 g every 12 hours IV (Lockman et al, 1984). Infections treated included pneumonia (20 patients), urinary tract infection (19 patients), soft tissue infection (7 patients), septic arthritis (2 patients), bacteremias (2 patients), and otitis media (1 patient). Microbiological cure was observed in 93% of infections.

Successful treatment of relapsing fever due to Borrelia crocidurae with 1 g ceftriaxone twice daily for 14 days was reported (Nassif et al, 1988). The patient had been initially

treated with penicillin, but failed to respond. As with infections caused by Borrelia burgdorferi (Lyme disease), ceftriaxone may be the drug of choice for infections due to Borrelia crocidurae (relapsing fever).

Ceftriaxone 37.5 mg/kg IV every 12 hours was effective in producing clinical and microbiologic cure in 19 of 21 children with severe bacterial infections (Harrison et al, 1983). Similar results were reported by other investigators, following administration of 25 to 37.5 mg/kg ceftriaxone IV every 12 hours in serious childhood infections or osteomyelitis (Chadwick et al, 1983). All patients were treated for at least 5 days. Clinical cure was observed in 31 of 34 children (91%), with a bacteriologic cure rate of 94%. Fourteen of 15 patients with CNS infections secondary to a variety of gram-positive and gram-negative organisms were cured.

Ceftriaxone 50 mg/kg IM or IV in single daily doses for 2 to 9 days was reported highly effective in the treatment of a variety of bacterial infections in children without meningitis (Congeni et al, 1985), producing satisfactory clinical response in 33 of 35 children.

Ceftriaxone 1 g daily was reported effective in the treatment of multidrug resistant salmonella osteomyelitis and prosthetic joint infection in a 33-year-old male (Sherman & Conte, 1987). The infecting organism (Salmonella heidelberg) was resistant to numerous antibiotics, including ampicillin, chloramphenicol and cotrimoxazole. Several months of therapy with ceftriaxone in addition to prosthesis removal resulted in clinical cure. Minimal inhibitory and minimal bactericidal concentrations of 0.12 mcg/mL were observed with tube dilution sensitivity testing of the organism. These data suggest the benefits of ceftriaxone in the treatment of salmonella infections.

The efficacy of ceftriaxone in 66 of 76 patients (87%) with osteomyelitis with ceftriaxone 1 g IV two times dialy or 2 g IV once daily in adults (50 mg/kg/day in children) (Eron et al, 1984). Nonresponding patients were primarily those with osteomyelitis complicated by vascular insufficiency. In this study, the authors emphasized that in 42 patients, once or twice daily dosing of ceftriaxone permitted cost-effective home therapy.

A single 125- or 250-mg IM dose of Ceftriaxone was effective in 100% of males with uncomplicated urethral or anorectal infections due to penicillinase-negative N gonorrhoeae (Hansfield & Murphy, 1983). In a subsequent study, clinical cure occurred in 54 of 55 (98%) women with uncomplicated gonorrhea with Ceftriaxone 125 mg IM as a single dose (Collier et al, 1984). In both studies, cure rates were similar to those observed with a single 2-g IM dose of Spectinomycin. Nine of 10 patients with pharyngeal gonococcal infections were cured with Ceftriaxone, as compared to 4 of 8 with Spectinomycin (Collier et al, 1984). Neither drug eradicated concurrent chlamydia trachomatis infection.

A 100% cure rate in 22 women with uncomplicated Endocervical Gonorrhea with a single 250-mg IM dose of Ceftriaxone was reported (Judson et al, 1983).

Ceftriaxone has proven effective in the treatment of lower respiratory tract infections in both adults and children (Scully & Neu, 1984; Maeson et al, 1984; Aronoff et al, 1983; Kovatch et al, 1983; Epstein et al, 1982; Fraschini et al, 1986; Rascio et al, 1985).

One report, recurrence of non-beta-lactamase-producing Moraxella catarrhalis (Branhamella catarrhalis) and Pseudomonas aeruginosa was frequent following treatment of acute purulent exacerbations of chronic bronchitis (Maesen et al, 1984).

40 children with radiologically proven pneumonia were treated at random with ceftriaxone (50 mg/kg/day) in a single IM dose or with amoxicillin (50 mg/kg/day orally three times daily) plus tobramycin (5 mg/kg/day orally three times daily). After 10 days of treatment, 20 of 20 children on ceftriaxone therapy and 18 of 19 children on the amoxicillin/tobramycin combination showed a complete resolution of the radiological picture. The authors conclude that monotherapy with ceftriaxone appears safe and effective in the treatment of pneumonia in children (Rascio et al, 1985).

Intramuscular ceftriaxone for 3 days eradicated organisms in 92 infants who previously failed on antibiotics for acute otitis media. Bacteriologic success occurred in 100% of

penicillin-susceptible streptococcus pneumonia and 82% of S pneumonia intermediately resistant to penicillin. Eradication rate was greater than 92% for H influenzae and S pyogenes (Leibovitz et al, 1998).

5.2 Pharmacokinetic properties:

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% lignocaine produces mean peak plasma concentrations of 40-70 mg/l within one hour. Bioavailability after intramuscular injection is 100%. Ceftriaxone is eliminated mainly as unchanged drug, approximately 60% of the dose being excreted in the urine and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10-22 ml/min. The renal clearance is 5-12 ml/min. A notable feature of ceftriaxone is its relatively long plasma elimination half-life of approximately 8 hours which makes single or once daily dosage of the drug appropriate for most patients.

5.3 Preclinical safety data

Preclinical data based on conventional studies on acute toxicity, repeated dose toxicity, reproduction toxicity and genotoxicity revealed no other special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Nil.

6.2 Incompatibilities

A possible disulfiram-like reaction may occur with alcohol.

6.3 Shelf-life

30 months.

6.4 Special precautions for storage

Store in a dry place, below 30^0C. Protect from light.

6.5 Nature and contents of container

Emceph Injection: 1 Vial of sterile Ceftriaxone Sodium USP with 1 ampoule Sterile Water for Injection USP

6.6 Instructions for use and handling

Store in a dry place, below 30°C. Protect from light.

Keep away from the reach of children.

Use immediately after preparation.

Follow the instructions given on the carton for intra-venous & intra-muscular use.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

A4-5319

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08-10-2010

10. DATE OF REVISION OF THE TEXT

Jan 2022