1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

1.1 (INVENTED) NAME OF THE MEDICINAL PRODUCT

International Non-Proprietary Name: Ceftriaxone and Sulbactam for Injection

1.2 STRENGTH

1.5 gm/vial

1.3 PHARMACEUTICAL FORM

Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 QUALITATIVE DECLARATION

Each Vial Contains:

Sterile Ceftriaxone Sodium USP

Equivalent to Ceftriaxone …… 1000 mg

Sterile Sulbactam Sodium USP

Equivalent to Sulbactam ……... 500 mg

Reconstituted Solution

Sterilised Water for Injections BP, 10 ml

2.2 QUANTITATIVE DECLARATION

Each combipack contains:

A. Each Vial Contains:

Sterile Ceftriaxone Sodium USP

Equivalent to Ceftriaxone …… 1000 mg

Sterile Sulbactam Sodium USP

Equivalent to Sulbactam ……... 500 mg

B. One Ampoule of Sterilised water for Injections BP 10 ml

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ceftriaxone & Sulbactam for Injection is indicated in infections caused by Ceftriaxone sodium-sensitive pathogens and may be used in the clinical settings in Sepsis, Meningitis, Abdominal Infections (e.g. Peritonitis, infection of the biliary tract), infections of the Bones, Joints, Soft tissue, Skin and of wounds, Renal and Urinary Tract Infections, Respiratory tract Infections, particularly Pneumonia, and Ear, Nose and Throat Infections, and uncomplicated gonorrhea.

Ceftriaxone & Sulbactam for Injection may also be used for Peri-operative Prophylaxis of Infections. A single dose given Preoperatively may reduce chances of Postoperative Infection.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Ceftriaxone and Sulbactam for Injection may be administered either by the intravenous route or intramuscularly.

Ceftriaxone & Sulbactam dose is based on equivalent of ceftriaxone dose (Ceftriaxone 1 gm is equivalent to Ceftriaxone and Sulbactam for Injection 1.5 gm).

Adults:

The usual adult daily dose in adults with normal renal function is equivalent to ceftriaxone 1 to 2 grams given once a day (or in two equally divided doses given 12 hr apart). The dose depends upon the type of infection and its severity. (The total daily Ceftriaxone dose should never exceed 4 grams)

Dosage of Ceftriaxone & Sulbactam in patients with renal impairment:

Dosage regimens of Ceftriaxone & Sulbactam For Injection should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30ml / min) to compensate for the reduced clearance of Sulbactam. Patients with creatinine clearance between 15 and 30 ml/min should receive a maximum of 1g of Sulbactam every 12 hours (maximum daily dosage of 2g Sulbactam). Patients with creatinine clearance of less than 15ml /min should receive 500mg Sulbactam every 12 hours.

Paediatric Patients:

For the treatment of skin and skin structure infections: The recommended total daily ceftriaxone (equivalent) dose is 50 to 75 mg/kg, once a day (or in two equally divided doses 12 hrs apart). The total daily dose should not exceed 1G. For the treatment of acute bacterial otitis media, a single IM ceftriaxone equivalent dose is 50 mg/kg (not to exceed 1 G). For the treatment of other serious infections (other than meningitis), the recommended total daily dose (equivalent to ceftriaxone) is 50 to 75 mg/kg, in two equally divided doses given every 12 hours. The total daily dose (equivalent to ceftriaxone) should not exceed 2G.

Meningitis:

It is recommended that the initial therapeutic dose (equivalent to Ceftriaxone) be 100 mg/kg (not to exceed 4 grams). The daily dose (in terms of ceftriaxone) may be administered once a day (or in two equally divided doses every 12 hours).

Generally ceftriaxone therapy should be continued for at least 2 days after recovery indicated by disappearance of the signs and symptoms of infection. The usual duration of therapy is 4 to 14 days although in complicated infections, one may need to treat for a longer period. When treating infections caused by Streptococcus pyrogens, therapy should be continued for at least 10 days. No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (e.g. Dialysis patients) and in patients with renal and hepatic dysfunctions.

4.3 CONTRAINDICATIONS

Ceftriaxone & Sulbactam for Injection is contraindicated in patients with known allergy to Cephalosporin group of antibiotics. Hypersensitivity to penicillin may pre-dispose the patient to the possibility of allergic cross-reactions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Superinfections with non-susceptible microorganisms may occur.

Since pseudo-membranous colitis has been reported to occur with ceftriaxone, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of Ceftriaxone & Sulbactam For Injection.

Ceftriaxone, if given at higher than standard doses, may get precipitated as its calcium salt in the gall bladder, the shadows of which seen under sonography, could be mistaken for gallstones. However, it is largely asymptomatic and the shadows disappear on discontinuation of therapy or in due course after the completion of therapy. Even in the case of symptomatic cases surgical interventions are not required, and they may be treated conservatively.

Discontinuation of Ceftriaxone & Sulbactam For Injection treatment in symptomatic cases is at the discretion of the clinician.

Like other cephalosporins, ceftriaxone is known to displace bilirubin from serum albumin. Hence caution needs to be exercised when considering Ceftriaxone & Sulbactam For Injection for the treatment of neonates with hyper-bilirubinemia.

In order to avoid the risk of development of bilirubin encephalopathy, use of Ceftriaxone & Sulbactam For Injection is best avoided in neonates in general and prematures in particular.

During prolonged treatment with Ceftriaxone & Sulbactam For Injection, blood profile should be checked at regular intervals.

Dosage adjustments are not necessary in hepatic failure. However, in patients with hepatic dysfunction and significant renal malfunction, Ceftriaxone & Sulbactam For Injection doses should not exceed an equivalent of 2g/day of Ceftriaxone. Close serum monitoring is recommended.

Extreme caution needs to be exercised in penicillin-sensitive patients. In case of serious hypersensitivity reactions, SC administration of epinephrine and other emergency measures are recommended.

The allergic reaction is the indication for the interruption of Ceftriaxone & Sulbactam For Injection therapy.

Ceftriaxone & Sulbactam For Injection should not be administered to neonates in general, hyperbilirubinemic neonates in particular, and to premature babies.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No impairment of renal function has been observed after concurrent administration of large doses of Ceftriaxone and potent diurectics.

There is no evidence to suggest that Ceftriaxone increases renal toxicity of aminoglycosides.

The elimination of Ceftriaxone is not altered by probenecid.

Ceftriaxone and chloramphenicol have been shown to be antagonistic in in vitro studies.

In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals.

Coombs test may show false-positive results during Ceftriaxone therapy.

Non-enzymatic urinary glucose estimation methods may give false-positive results.

4.6 PREGNANCY AND LACTATION

Reproductive studies on ceftriaxone have been performed in mice and rats at very high doses. No evidence of embryotoxicity, fetotoxicity or teratogenicity was observed. However, in absence of adequate and well- controlled studies in pregnant women, and since reproductive animal studies may not always reflect human response, this drug should be used during pregnancy only if clearly needed. As ceftriaxone is secreted in the breast-milk, albeit at low concentrations, caution should be exercised in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None stated

4.8 UNDESIRABLE EFFECTS

The following side effects, reported to occur during Ceftriaxone therapy, may be seen with the combination as well:

Gastrointestinal: Diarrhoea, nausea & vomiting (less frequent), stomatitis, and glossitis.

Hepatic: Elevations of SGOT/SGPT.

Hematological: Eosinophilia, thrombocytopenia, leukopenia, granulocytopenia, hematoma or bleeding. Hemolytic anemia is observed less frequently. Agranulocytosis (< 500/mm 3) has been reported occasionally at a total cumulative dose exceeding 20 g.

Skin reactions: Exanthema, allergic dermatitis, pruritis, urticaria, edema, erythema multiforme.

Other side effects such as headache, dizziness, increase in serum creatinine, mycosis of the genital tract, oliguria, fever, and shivering have been observed.

Anaphylactic shock may occur which requires immediate counter-measures.

Local reactions:

Pain, induration, and tenderness may be encountered in a small number of patients.

Inflammatory reactions in the vein wall may also occur after IV administration. These may be minimized by slow injection, given over 2 to 5 minutes.

4.9 OVERDOSE

Limited information is available on the acute toxicity of Ceftriaxone & Sulbactam For Injection. No specific antidote is available for the treatment of overdose. Hemodialysis does not remove the drug from system effectively. Hence, the treatment for Ceftriaxone & Sulbactam for Injection overdose is essentially supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Combinations of Cephalosporin and beta-lactamase inhibitors;

Mode of action

Ceftriaxone is a beta-lactam antibiotic like the penicillins with bactericidal action. Penicillin-binding proteins (PBPs) are responsible for several steps in the synthesis of the cell wall of bacteria and are found in large quantities (several hundred to several thousand molecules/bacterial cell). Ceftriaxone inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to the specific PBPs located inside the bacterial cell wall. Ceftriaxone interferes with PBP-mediated cell wall synthesis leading to cell lysis, which is mediated by bacterial cell wall autolytic enzymes (autolysins), possibly through interference with an autolysin inhibitor. The presence of an aminothiazolylacetyl side chain with an alpha methoxyimino group at the 7-position of the beta-lactam ring provides Ceftriaxone with enhanced antibacterial activity, particularly against the Enterobacteriaceae (e.g., E. coli, Klebsiella, Proteus, and Serratia) and increased stability against many of the beta-lactamases. Many strains of Pseudomonas aeruginosa are susceptible to Ceftriaxone. Other susceptible gram-negative organisms include Enterobacter, Citrobacter, Morganella, Providencia, Moraxella (Branhamella) catarrhalis, and N. meningitidis. Ceftriaxone has exceptional activity against H. influenzae and N. gonorrhoeae and is the drug of choice for uncomplicated N. gonorrhoeae infections. It has no activity against B. fragilis but is active against many other anaerobes.

However, recently it has been observed that the bacteria, through formation of betalactamases hydrolyze the beta-lactam ring of cephalosporins to inactivate them, thereby developing resistance to the drug. Recently, such a development of resistance to ceftriaxone has been observed, which can be judged by an increase in the MIC.

Sulbactam, by irreversibly binding to the beta-lactamases produced by the common gram-positive or negative bacteria protects the beta-lactam ring of ceftriaxone, and conserves the activity. Thus on combining ceftriaxone with sulbactam, the combination product - Ceftriaxone & Sulbactam For Injection extends its utility in the treatment of broad range of infections caused by organisms resistant to the antibiotic alone, making them susceptible, possibly through lowering of MIC.

5.2 PHARMACOKINETIC PROPERTIES

Ceftriaxone is completely absorbed with peak plasma concentrations of 40mcg/ml and 80mcg/ml at 2 to 3 hours after IM injection of 500mg and 1g dose of Ceftriaxone respectively. It follows a dose dependent non-linear pharmacokinetic because of the high (80-85%) plasma protein. A similar AUC is observed after administration of an equivalent dose of Ceftriaxone by the IM or IV route. Widely distributed in body tissues and fluid, it crosses the inflamed as well as non-inflamed meninges and may achieve therapeutic concentrations in the CSF.

Irrespective of the dose Ceftriaxone has a half-life of between 6 to 9 hours. The half-life may be prolonged in neonates. While moderate renal impairment may not affect the halflife of Ceftriaxone appreciably, severe renal impairment does, with a longer half-life, which is further increased if accompanied with liver impairment. Ceftriaxone at 1 - 2 g dose achieves concentrations above the MICS in the lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone; and cerebral, pleural, prostatic and synovial fluids for most of the pathogens responsible for infection, even after more than 24 hours.

Urinary excretion by glomerular filtration accounts for 50-60% of the elimination. The intestinal flora has been shown to convert ceftriaxone into inactive metabolites. Biliary route accounts for 40-50% of excretion. In case of renal impairment the biliary excretion may be

the major pathway for excretion. In Infants& Children: Elimination half-life in neonates is prolonged which decreases with increasing postnatal age. In infants aged less than 8 days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 - 3 times that seen in the adults.

In patients with renal failure, non-renal elimination may compensate. Sulbactam has a half-life of about 1 hour in healthy volunteers. Serum concentrations reached are proportional to the dose administered. It is predominantly eliminated through kidney in the unchanged form.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

6.2 INCOMPATIBILITIES

No impairment of renal function has been observed after concurrent administration of large doses of Ceftriaxone and potent diurectics.

There is no evidence to suggest that Ceftriaxone increases renal toxicity of aminoglycosides. The elimination of Ceftriaxone is not altered by probenecid. Ceftriaxone and chloramphenicol have been shown to be antagonistic in in vitro studies. In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals. Coombs test may show false-positive results during Ceftriaxone therapy. Non-enzymatic urinary glucose estimation methods may give false-positive results.

6.3 SHELF LIFE

24 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC in a dry place. Protect from light.

KEEP OUT OF REACH OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

20 ml Plain Glass vial (USP Type- I) with Diluents (Sterilised Water for Injections BP, 10 ml) packed in a carton along with plastic tray and insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not Applicable