1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals

1.3.1.1 Invented Name of the Medicinal Product

SALBACEF

Ceftriaxone and Sulbactam for Injection

1.3.1.2 Strength

Ceftriaxone Sodium USP

Equivalent to Ceftriaxone……1000 mg

Sulbactam Sodium USP

Equivalent to Sulbactam …….500 mg

1.3.1.3 Dosage Form

Parenteral

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Combipack Contains:

1) Each vial contains:

Ceftriaxone Sodium USP

Eq. to Ceftriaxone …….1000 mg

Sulbactam Sodium USP

Eq. to Sodium…….500 mg

2) One Ampoule of Sterilised water for Injections BP 10 ml.

1.3.1.5 PHARMACEUTICAL FORM

Injection

White to off white crystalline powder filled in clear glass vial, sealed with grey coloured butyl rubber plugs with coloured flip off seal.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1Therapeutic indications

Ceftriaxone and Sulbactam for Injection are indicated for the treatment of the following infections when caused by susceptible bacteria:

- Meningitis
- For treatment of Nosocomial infections surgical prophylaxis
- Urinary tract infections (complicated by underlying urological abnormalities)
- Skin and soft tissue infections Like cellulites, erysepalis etc.
- Cholecystitis
- Osteomyelitis
- Sexually transmitted diseases (Gonorrhoea, Chancroid, Syphilis)
- Chronic suppurative bacterial otitis media
- Infections in dialysis unit

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults

The usual adult daily dose (in terms of Ceftriaxone) is 1-2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

Dosage regimen for Ceftriaxone-Sulbactam should be adjusted in patients with marked decrease in renal function (creatinine clearance of <30ml/min) and to compensate for reduced clearance less than 15ml/min patient should receive a maximum of 500mg of sulbactam every 12 hours (maximum dose 1 gram of sulbactam)

Paediatric patients

For treatment of Skin and Soft tissue infections the recommended total daily dose (in terms of Ceftriaxone) is 50-75mg/kg given once a day or (in equally divided doses twice a day). The total daily dose should not exceed 1 gram.

For treatment of acute bacterial otitis media: A single intramuscular dose of 50 mg/kg (not to exceed 1gram) is recommended.

In treatment of Meningitis: The initial therapeutic dose in terms of Ceftriaxone should be 100 mg/kg (not to exceed 4 grams) Daily dose may be administered once a day or in equally divided doses 12 hourly. The usual duration of therapy is 7-14 days.

For treatment of serious infections other than meningitis: Recommended total daily dose in terms of Ceftriaxone is 50-75 mg/kg given in divided doses every 12 hours. The total daily dose (in terms of Ceftriaxone) should not exceed more than 2 grams

1.3.1.6.3 CONTRAINDICATIONS

Ceftriaxone-Sulbactam is contraindicated in patients with known allergy to penicillins and cephalosporins.

1.3.1.6.4 WARNING AND PRECAUTIONS

Warnings

Serious or occasionally fatal anaphylactic reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of hypersensitivity reactions to multiple allergens. Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Precautions

General

Transient elevations of BUN and serum creatinine have been observed, at recommended doses, the nephrotoxic potential of ceftriaxone is same as other cephalosporins. Since Ceftriaxone is excreted both via renal and bile patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone are administered.

Dosage adjustments are not necessary in patients with hepatic dysfunction; however in patients with both renal failure and hepatic dysfunction, dosage should not exceed more than 2 g daily with close monitoring of serum concentrations

Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis

Considering the maximum duration of treatment and the class of the compound, carcinogenic studies with Ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis

Genetic toxicological tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured in vitro with

Ceftriaxone. Ceftriaxone showed no potential mutagenic activity in these studies

Impairment of fertility

Ceftriaxone produced no impairment in fertility when given intravenously to rats at daily doses upto 586 mg/kg/day, approximately 20 times the recommended dose of 2 gm/day.

Pregnancy

Teratogenic effects: Pregnancy category B. Reproductive studies have been performed in mice and rats at doses upto 20 times the usual human dose and no evidence of embryo toxicity, fetotoxicity or teratogenicity. In primates no teratogenicity or embryogenicity was demonstrated at a dose approximately 3 times the human dose.

There are however no well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers

Low concentrations of Ceftriaxone are excreted in human milk. No risks to nursing infants have been reported but caution should be exercised when ceftriaxone-sulbactam is administered to nursing women.

Paediatric use

Ceftriaxone-Sulbactam should not be administered to hyperbilirubinemic neonates, especially premature.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

If taken with other drugs or over the counter products, the effects of Ceftriaxone Sulbactam Injection may change. This may increase risk for side-effects or the drug may not work properly. Ceftriaxone Sulbactam Injection may interact with the following drugs and products:

- Alcohol
- Allopurinol
- Aminosyn
- Calcium chloride
- Calcium gluceptate
- Calcium gluconate
- Kabiven
- Leucovorin
- Probenecid
- Procalamine
- Tetracyclines
- Levoleucovorin calcium

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy:

Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses upto 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity, teratotoxocity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.

In rats in the segment I (fertility and general reproduction) and segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers

Low concentrations of ceftriaxone are excreted in human milk. No risk to nursing infants has been reported but caution should be exercised when ceftriaxone is administered to a nursing woman.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Data not available.

1.3.1.6.8 UNDESIRABLE EFFECTS

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

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

Hepatic: Elevations of SGOT/SGPT.

Hematological: Eosinophilia, thrombocytopenia, leucopenia, granulocytopenia, hematoma or bleeding. Hemolytic anemia is observed less frequently. Agranulocytosis (<500/mm3) has been reported occasionally at a total cumulative dose exceeding 20g.

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 required immediate counter-measures.

1.3.1.6.9 OVERDOSE

Limited information is available on the acute toxicity of Ceftriaxone-Sulbactam. There is no specific antidote. If acute overdosage of Ceftriaxone-Sulbactam occurs, supportive and symptomatic treatment should be initiated. Hemodialysis or Peritoneal dialyses are ineffective in reducing ceftriaxone concentration following overdosage.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacotherapeutic group: Antibacterial

Mechanism of action:

The bactericidal activity of Ceftriaxone and Sulbactam for injection 1.5 g is due to the Ceftriaxone component and the ability of Ceftriaxone to interfere with the biosynthesis of the peptidoglycan component of the bacterial cell wall by binding to and inactivating penicillin-binding proteins (PBPs).

Ceftriaxone induces filamentation in *Escherichia coli* and *Pseudomonas aeruginosa*, it binds primarily to PBP 3 which is responsible for formation of cross-wall or septum of dividing bacilli.

Ceftriaxone has a high degree of stability against the beta-lactamases, both penicillinases and cephalosporinases produced by both gram -ve and gram +ve bacteria but not against chromosomally and plasmid mediated ESBL's produced by some strains of *Klebsiella, Escherichia coli, Enterobacter spp* and *Serratia spp*.

Sulbactam irreversibly blocks the destruction of beta-lactam ring of Ceftriaxone

by these wide variety of ESBLs and chromosomally mediated beta-lactamases by attaching to these enzymes and acting as a suicide substrate that forms a stable intermediate, rendering the enzyme inactive.

Sulbactam is a broader-spectrum beta-lactamase inhibitor than clavulanic acid. Sulbactam does not induce chromosomal beta-lactamases like clavulanic acid, nor does it select for derepressed beta-lactamase-producing bacteria. Thus the full potential of Ceftriaxone against *Klebsiella, pseudomonas, Eschericia coli spp* is restored by addition of Sulbactam.

Spectrum of Ceftriaxone and sulbactam for injection 1.5 g

The combination of Ceftriaxone sodium and Sulbactam sodium is active against all the organisms sensitive to Ceftriaxone. In addition it demonstrates synergistic activity (reduction in minimum inhibitory concentrations, for the combination versus those of each component) in a variety of organisms.

Gram-Negative Aerobes

Acinetobacter calcoaceticus

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)

Haemophilus parainfluenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Moraxella catarrhalis (including beta-lactamase producing strains)

Morganella morganii

Neisseria gonorrhoeae (including penicillinase - and nonpenicillinase producing strains)

Neisseria meningitidis

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*. Many strains of the above organisms that are resistant to other antibiotics, eg, penicillins, cephalosporins and aminoglycosides, are susceptible to Ceftriaxone.

Ceftriaxone also demonstrates in vitro activity against most strains of the following microorganism like *Citrobacter diversus , Citrobacter freundii,*

Providencia species (including *Providencia rettgeri , Salmonella* species

(including *S. typhi*), *Shigella* species

Gram-Positive Aerobes

Staphylococcus aureus (including penicillinase-producing strains and methicillin sensitive strains but not methicillin resistant strains)

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus pyogenes

Viridans group streptococci

Anaerobes:

Bacteroides fragilis, Clostridium species, Peptostreptococcus species

1.3.1.7.2 Pharmacokinetic properties

Ceftriaxone and Sulbactam for injection can be administered Intramuscularly or Intravenously.

Following intramuscular administration, peak serum concentrations of Ceftriaxone and Sulbactam are seen between 15 minutes to 2 hrs.

The maximum plasma conc. of Ceftriaxone after a single IM dose of 1.0 g is about 81mg/L and is reached 2-3 hrs after the dose while that of Sulbactam sodium is 6-24 mg/L and is reached approximately 1 hr after the dose. Hence effective amount of beta-lactamases are destroyed by the time peak concentration of Ceftriaxone is reached allowing full potential of action of Ceftriaxone against ESBL producing *Klebsiella*, *E coli spp*. Serum concentrations have been shown to be proportional to the amount of dose administered.

The area under curve (AUC) after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone sodium.

On intravenous administration Ceftriaxone sodium diffuses into the tissue fluid where if given in the recommended doses bactericidal concentrations are maintained for upto 24 hrs. Ceftriaxone is highly bound to human serum protein by about 83-90%.

Distribution

The volume of distribution of Ceftriaxone sodium is 7-12 L and that of Sulbactam is 18-27.6 L.

Ceftriaxone sodium penetrates well into the extravascular spaces, tissue fluid and the synovial fluid of inflamed joints. The concentrations in most extracellular foci reach or exceed several times the MIC of most pathogens for at least 24 hours after a single administration.

Ceftriaxone sodium reaches therapeutically effective concentrations in patients with bacterial meningitis which are at least ten-fold the MICs of common pathogens such as, *Enterobacteriaceae, H.influenzae*, *Meningococci*, *Pneumococci* and Group B *Streptococci*.

Ceftriaxone crosses placenta and is distributed in the amniotic fluid. It is also distributed in the milk.

Metabolism and excretion

Ceftriaxone is not metabolised in the body and is eliminated unchanged via two pathways, urine and bile. 40-50% of parenterally administered dose is excreted into the urine within 48 hours as active drug. Thus, high concentrations are attained in urine, whatever is not excreted via kidney is excreted through bile.

Metabolism of sulbactam is less than 25%. 70-80% of Sulbactam is excreted by the kidney biliary excretion is minimal and. renal excretion is blocked by probenecid. Sulbactam and Ceftriaxone can be removed by hemodialysis.

Impaired renal function and Hepatic insufficiency: Ceftriaxone is excreted via both renal and biliary pathways therefore patients with renal failure normally require no adjustments of dose however concentration of the drug should be monitored in such patients and if there is evidence of drug accumulation then dosage adjustments should be made accordingly. Dosage adjustments are not necessary in patients with hepatic dysfunction, however in patients with both hepatic dysfunction and significant renal failure, dosage should not exceed more than 2 gm daily with close monitoring of serum concentrations

1.3.1.7.3 Preclinical safety data

Data not available

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Not applicable.

1.3.1.8.2 Incompatibilities:

Not applicable.

1.3.1.8.3 Shelf life:

24 Months.

1.3.1.8.4 Special precautions for storage:

Store below 30°C. Protected from light.

1.3.1.8.5 Nature and contents of container:

Ceftriaxone and Sulbactam for Injection is filled in 20 ml Transparent Flint glass vial USP type-III, free from pyrogens. The container is closed by 20 mm grey butyl rubber stoppers (pre-autoclaved) and finally sealed with 20 mm colored flip off seal.

1.3.1.8.6 Special precautions for disposal and other Special handling:

Not Applicable

1.3.1.9 Marketed by:

AQUATIX PHARMACEUTICALS LIMITED.

No. 14, Prince Bode Oluwo Street,

Mende, Maryland,

Lagos, Nigeria.

1.3.1.10 Manufactured by:

ZEISS PHARMACEUTICALS PVT LTD

Plot no. 72, EPIP-1,

Jharmajri Baddi, Dist-Solan, H.P.