1.3 Product Information

1.3.1 Summary Product Characteristics (SmPC)

1.31.1 Product information for Health Professionals (For All Products subject to Medical Prescription)

1. NAME OF THE MEDICINAL PRODUCT

ANNXONE-S (Ceftriaxone and Sulbactam for injection 1.5gm)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Sterile Ceftriaxone Sodium USP	
Equivalent to Ceftriaxone Anhydrous	1000 mg
Sterile Sulbactam sodium USP	
Equivalent to Sulbactam Anhydrous	500 mg

3. PHARMACEUTICAL FORM

Sterile powder for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As mention below:

Infections caused by pathogens sensitive to Ceftriaxone Injection, e.g.:

- sepsis;
- meningitis;
- abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);
- infections of the bones, joints, soft tissue, skin and of wounds;
- infections in patients with impaired defense mechanisms;
- renal and urinary tract infections;
- respiratory tract infections, particularly pneumonia, and ear, nose and throat infections;
- genital infections, including gonorrhea.

Perioperative prophylaxis of infections.

POSOLOGY AND METHOD OF ADMINISTRATION

ANNXONE-S is a combination of Ceftriaxone sodium and Sulbactam Sodium available forparenteral 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 ANNXONE-S (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 50mg/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

4.3 Contraindications

Ceftriaxone Injection is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics. In patients hypersensitive to penicillin, consider the possibility of allergiccross-reactions.
The use of sulbactam is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillin's.

4.4 Special warnings and precautions for use

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction
4.6. Pregnancy and Lactation

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

embryogenicitywas 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 risk to nursing infants have been reported but caution should be exercised when Ceftriaxone sulbactam is administered to nursing women.

Paediatric use

Triaxone-s (Ceftriaxone-Sulbactam) should not be administered to hyperbilirubinemic neonates, especially premature.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

4.9 Overdose

NA

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action:

The bactericidal activity of Triazone-s 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, Enterobacterspp 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 Sulbatam.

5.2 Pharmacokinetic Properties:ANNXONE-S can be administered IM or IV.

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 dsoe 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 parent rally 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.
Safety profile : Clinical studies of the combination of sulbactam plus beta-lactam antibiotics or penicillin's have revealed no major hematologic, renal, hepatic, or central nervous system reactions. Diarrhea has not been a major problem after intravenous use.
Incidence of side-effects due to Ceftriaxone is as follows: G.I. effects- 2-3%, cutaneous reactions 1-3%, haemotological 1-2%, miscellaneous 1.5-3%

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NA

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep in dry place and at a temperature not exceeding 25^0C.

6.5 Nature and contents of container

15 ml flint vial USP Type III

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

20.08.2018