1.17 Summary product characteristics (SPC)
Enclosed

Summary of Product Characteristic

1. NAME OF THE MEDICINAL PRODUCT

XONE SB 1500 (Ceftriaxone and Sulbactam for Injection 1.5 gm)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredients	Spec.	Overages	Unit Formula (mg)	Batch Formula (kg)
1.	Sterile Blend of Ceftriaxone and Sulbactam	USP	-	1500 mg*	15**

*Fill weight is calculated on the basis of potency of Raw material.
** Standard batch size is fixed as per raw material canister size.(i.e. 10000 vials from 10 kg of canister)

No Excipients are used in this formulation.

3. PHARMACEUTICAL FORM

Dry Powder For Injection
Description: Off white to pale yellow crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Sulbaxone 1.5 gm, dry powder for Injection is indicated in in infections caused by Ceftriaxone sodiumsensitive 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.

Method of administration
It can be administered IM or IV.

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. Special warnings and precautions for use

4.4 Interaction with other medicinal products and other forms of interaction

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.

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.

4.5 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.

4.6 Effects on ability to drive and use machines

Ceftriaxone has been associated with dizziness, which may affect the ability to drive or operate machinery.

4.7 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.

4.8 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 Pharmacodynamics 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 betalactamases. 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.

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 18-27.6L.
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.

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 halflife 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.

5.3 Preclinical safety data

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.

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.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

20 ml, USP type III, clear glass vial closed with bromo butyl rubber stopper and sealed with flip off seal

6.6 Special precautions for disposal <and other handling>

After 24 hours any unused solution should be discarded.
The reconstituted solution should be clear. Do not use if particles are present.
For single use only. Discard any unused contents.
Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely.

7. APPLICANT/MANUFACTURER

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