SUMMARIES OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented name of the medicinal product:

BAXCEF-SB (Ceftriaxone and Sulbactam for Injection 1.5g)

1.2 Strength:

1.5g

1.3 Pharmaceutical Form:

Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains:

Ceftriaxone Sodium USP (Sterile) Equivalent to Ceftriaxone..... 1000 mg

Sulbactam Sodium USP (Sterile) Equivalent to Sulbactam..... 500 mg

3. PHARMACEUTICAL FORM

Powder for injection

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

It is indicated for the treatment of the following infections when caused by susceptible bacteria.

- Lower respiratory Tract Infections.
- Acute Bacterial Otitis Media.
- Skin and Skin Structure Infections.
- Urinary Tract Infections [complicated and uncomplicated].
- Pelvic Inflammatory Disease.
- Bacterial Septicemia.
- Bone and Joint Infections.
- Intra-Abdominal Infections.

- Meningitis.
- Sexually transmitted disease.
- Surgical Prophylaxis.

The preoperative administration of BAXCEF-SB may reduce the incidence of postoperative infections in patients undergoing surgical procedures.

4.2 Posology and method of administration

BAXCEF-SB may be administered intravenously or intramuscularly.

Reconstitution: Following are the recommendation for diluting the solution.

Vol. of WFI required to prepare solution		
	For I.M. Use	For I.V. Use
BAXCEF-SB 1.5g	5 ml	10 ml
BAXCEF-SB 750mg	2 ml	5 ml
BAXCEF-SB 375mg	1 ml	3 ml
BAXCEF-SB KID	0.5 ml	1.5 ml

Dosage:

Adults:

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

Paediatric Patients:

For the treatment of skin and skin structure infections, the recommended daily dose [in terms of ceftriaxone] is 50 to 75 mg/kg given once a day or in [equally divided doses twice a day]. The total daily dose should not exceed 1 gm. For the treatment of acute bacterial otitis media, a single intramuscular dose [in terms of ceftriaxone] of 50 mg/kg (not to exceed 1 gram) is recommended.

For the treatment of serious miscellaneous infections other than meningtis, recommended total daily dose [in terms of ceftriaxone is 50 to 75 mg/kg, in divided doses every 12 hours. The total daily dose in terms of ceftriaxone should not exceed 2 grams.

In the treatment of meningitis, it is recommended that the initial therapeutic dose in terms of Ceftriaxone be 100 mg/kg [not to exceed 4 grams]. Thereafter, a total daily dose of 100 mg/kg.day (not to exceed 4 g) daily is recommended. The daily dose [in terms of ceftriaxone may be administerd. once a day [or in equally divided doses every 12 hours]. The usual duration of therapy in meningitis is 7 to 14 days. Generally, ceftriaxone therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infection longer therapy may be required.

When treating infections caused by Streptococcus pyogenes, therapy should be continued for at least 10 days. No dosage adjustment is necessary for patients with impairment of renal and hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e.g.Dialysis patients) and patients with both renal and hepatic dysfunctions.

4.3 Contraindications

BAXCEF-SB is contraindicated in patients with known allergy to penicillins or cephalosporins or any ingredients of BAXCEF-SB.

4.4 Special warning and Precautions for use.

Intrathecal anaesthesia should only be undertaken by clinicians with the necessary knowledge and experience.

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Resuscitative equipment and drugs should be immediately available and the anaesthetist should remain in constant attendance.

Intravenous access, e.g. an i.v. infusion, should be in place before starting the intrathecal anaesthesia. The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with the diagnosis and treatment of side effects, systemic toxicity and other complications. If signs of acute systemic toxicity or total spinal block appear, injection of the local anaesthetic should be stopped immediately.

Like all local anaesthetic drugs, bupivacaine may cause acute toxicity effects on the central nervous and cardiovascular systems, if utilised for local anaesthetic procedures resulting in high blood concentrations of the drug. This is especially the case after unintentional intravascular administration or injection into highly vascular areas.

Ventricular arrhythmia, ventricular fibrillation, sudden cardiovascular collapse and death have been reported in connection with high systemic concentrations of bupivacaine. Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts. High systemic concentrations are not expected with doses normally used for intrathecal anaesthesia. There is an increased risk of high or total spinal blockade, resulting in cardiovascular and respiratory depression, in the elderly and in patients in the late stages of pregnancy. The dose should therefore be reduced in these patients.

Intrathecal anaesthesia with any local anaesthetic can cause hypotension and bradycardia which should be anticipated and appropriate precautions taken. These
may include preloading the circulation with crystalloid or colloid solution. If hypotension develops it should be treated with a vasopressor such as ephedrine 10–15 mg intravenously.

Severe hypotension may result from hypovolaemia due to haemorrhage or dehydration, or aorto-caval occlusion in patients with massive ascites, large abdominal tumours or late pregnancy. Marked hypotension should be avoided in patients with cardiac decompensation. Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during intrathecal anaesthesia.

Intrathecal anaesthesia can cause intercostal paralysis and patients with pleural effusions may suffer respiratory embarrassment. Septicaemia can increase the risk of intraspinal abscess formation in the postoperative period.

Neurological injury is a rare consequence of intrathecal anaesthesia and may result in paraesthesia, motor weakness and paralysis. Occasionally these are permanent.

Before treatment is instituted, consideration should be taken if the benefits outweigh the possible risks for the patient.

Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver or renal dysfunction require special attention, although regional anaesthesia may be the optimal choice for surgery in these patients.
Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

4.5 Interactions with other medicinal products and other forms of interaction
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially, of one another, if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.
The elimination of ceftriaxone is not altered by probenecid.

Aminoglycoside antibiotics and diuretics: No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g.furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides.

Alcohol: No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.

Antibiotics: In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Anticoagulants: As ceftriaxone has an N-methylthiotriazine side-chain, it might have the potential to cause hypoprothrombinaemia resulting in an increased risk of bleeding in patients treated with anticoagulants.

Oral Contraceptives: Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.
Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Interference with Laboratory Tests: In patients treated with ceftriaxone, the Coombs' test may in rare cases be false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods such as copper reduction methods (Benedict's, Fehling's or Clinitest) for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be carried out enzymatically.

4.6 Pregnancy and Lactation

Pregnancy

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

In rats, during studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behaviour 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.

Lactation

Low concentrations of ceftriaxone are excreted in human milk hence caution should be exercised when ceftriaxone is administrated to a nursing woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Gastro-intestinal complaints: Loose stools/diarrhoea, nausea, vomiting, stomatitis, glossitis.

Haematological changes: Eosinophilia, haematoma or bleeding, thrombocytopenia, neutropenia, leukopenia, granulocytopenia and haemolyticanaemia. Isolated cases of agranulocytosis (<500/mm^3) have been reported, most of them following total doses of 20 g or more. Exanthema, allergic dermatitis, pruritus, urticaria, oedema, erythema multiforme may occur.

Other side effects include headaches and dizziness, increase in liver enzymes, oliguria, and increase in serum creatinine, mycosis of the genital tract, fever, shivering and anaphylactic or anaphylactoid reactions.

4.9 Overdose

Limited information is available on the acute toxicity of Ceftriaxone / Sulbactam. There is no specific antidote. If acute overdosage of BAXCEF-SB occurs, supportive and symptomatic treatment should be initiate. Haemodialysis or Perotoneal dialyses are ineffective in reducing ceftriaxone concentration following over dosage.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

For Ceftriaxone Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins, ATC code: J01DD04 and for Sulbactam Pharmacotherapeutic group: beta-lactamase inhibitor, ATC code: J01CG01.

The antibacterial component of BAXCEF-SB is due to the inhibition of cell wall synthesis attained by ceftriaxone. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases of gram-negative and positive bacteria. But chromosomally medicated enzymes though less common can be induced in some strains of Klebsiella, Enterobacter and Serratia species.

Sulbactam in BAXCEF-SB is a potent, highly specific inhibitor or a wide variety of beta lactamases produced by common gram-negative and gram-positive aerobes. By forming a protein complex with beta-lactamases Sulbactam irreversibly blocks their destructive hydrolytic activity. Thus the full potential of ceftriaxone against Enterobacter and Pseudomonas species is restored by the addition of Sulbactam. the combination of Sulbactam and ceftriaxone sodium is active against all the organisms sensitive to Ceftriaxone.

MICROBIOLOGY

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, kebsiella pneumonia, Moraxella catarrhalis* including *beta lactamase* producing strains. *Morganellia Morganii, Neisseria gonorrhoeae [*including *penicillianase-and nonpenicillinase-producing strains]. Neisseria meningitidis, Proteus vulgaris, Serratia marcescens* and also many strains of *Pseudomonas aeruginosa.*

Gram-Positive Aerobes:

*Staphylococcus aureus [*including *penicillinase-producing strains]. Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes* and *Viridans* group of *streptococci*.

Anaerobes:

Bacteroides fragilis, Clostridium species, Peptostreptococcus species.

5.2 Pharmacokinetic properties

Following intramuscular administration, peak serum concentrations of Sulbactam and ceftriaxone are seen between 15 minutes to 2 hours. The maximum plasma concentration of ceftriaxone after a single IM dose of 1g is about 81 mg/L and is reached in 2-3 hours after the dose, while that of Sulbactam sodium is 6-24 mcg/ml and is reached approximately in1 hour in healthy volunteers. Serum concentrations have shown to be proportional to the dose administered. The area under the plasma concentrations-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone. On intravenous administration, ceftriaxone diffuses into the tissue fluid, where, if it is given in the recommended dosage range, bactericidal concentrations lasting upto 24 hours may be maintained.

Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentrations eg. from 95% binding at plasma concentrations < 100 mg/L to 85% binding at 300 mg/L. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

The volume of distribution of ceftriaxone is 7-12 L and that of Sulbactam is 18-27.6 L. Both are widely distributed into body tissues and fluids.Ceftriaxone crosses placenta and is distributed in the amniotic fluid. It is also distributed in milk. In healthy, young adult volunteers, the total plasma clearance is 10-22 mL/min. The renal clearance is 5-12 mL/min. Approximately 75-85% of Sulbactam and 50-60% of ceftriaxone is excreted unchanged in the urine, while the remaining dose is excreted in the bile.

The mean plasma elimination half-life of ceftriaxone is 8 hours in healthy, young adult volunteers. In neonates, urinary recovery accounts for about 70% of the dose. In infants aged less than eight days and in elderly persons aged over 75 years, the average elimination half-life

is usually 2-3 times that in the young adult group. The mean serum half life of sulbactam is approximately 1 hour.

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and elimination half life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

In patients with different degrees of renal function administered with Sulbactam/ Ceftriaxone combinations, the total body clearance of Sulbactam is correlated with estimated creatinine clearance. Patients, who are functionally anephric, show a significantly longer half-life of Sulbactam [mean 6.9 and 9.7 hours in separate studies].

Haemodialysis significantly alters the half-life, total body clearance and volume of distribution of Sulbactam. Studies conducted in paediatrics have shown no significant changes in pharmacokinetics of the components of ceftriaxone and Sulbactam, compared to adult values. There is no evidence of any pharmacokinetic drug interaction between Sulbactam and ceftriaxone when administered together.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

No excipients are used in manufacture of BAXCEF-SB (Ceftriaxone & Sulbactam for Injection 1.5g).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C, Protected from light & moisture.

6.5 Nature and contents of container

20 ml flint USP type I, glass vial, plugged with grey bromo butyl rubber plug & sealed with dark pink coloured flip off aluminium seal & packed in a mono carton along with its package insert.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER:

MANUFACTURED BY:

KILITCH DRUGS INDIA LTD

Plot no - C-301/2, M.I.D.C ,T.T.C Indl. Area, Pawane, Navi Mumbai - 400705, Maharashtra, INDIA.

8. DATE OF REVISION OF THE TEXT:

Not Applicable.

The Summary of Product Characteristics (SPC) is satisfactory.

9. DOSIMETRY (IF APPLICABLE):

Not Applicable.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable.