Summaries of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

BAXCEF (Ceftriaxone for Injection USP 1g)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains:

Sterile Ceftriaxone Sodium Equivalent to Ceftriaxone Anhydrous USP.....1 g

Sr. No.	Ingredient	Specification	Label Claim/ Vial	Qty. /Vial
1	Sterile Ceftriaxone Sodium Equivalent to Ceftriaxone Anhydrous	USP	1 g	1 g

3. PHARMACEUTICAL FORM:

Powder for Injection

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Lower Respiratory Tract Infection

Etiology - Strep. Pneumoniae, other streptococci exclusive of Enterococci, Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella spp. (including K. pneumoniae), E. coli, E. aerogenes, P. mirabilis and S. marcescens.

Skin and Skin Structure Infections

Etiology - Staph. aureus, Staph. epidermidis, streptococci (excluding Enterococci), E. cloacae, Klebsiella spp. (including K. pneumoniae), P.mirabilis and Ps. aeruginosa.

Urinary Tract Infections (complicated and uncomplicated)

Etiology - E. coli, P. mirabilis, P. vulgaris, M. morganil and Klebsiella spp. (including K. pneumoniae)

Uncomplicated Gonorrhoea - Cervical / Urethral / Rectal

Etiology - N. gonorrhoea including penicillinase producing strains.

Pelvic Inflammatory Disease

Etiology - N. gonorrhoea

Bacterial Septicemia

Etiology - S. aureus, Strep. pneumoniae, E. coli, H. influenzae and K. pneumoniae.

Bone and Joint infections

Etiology - S. aureus, Strep. pneumoniae, streptococci other than Enterococci, E. coli, P. mirabilis, K. pneumoniae and Enterobacter spp.

Intra-Abdominal Infections

Etiology - E. coli, K. pneumoniae

Meningitis

Etiology - H. influenzae, N. meningitides and Strep. pneumoniae, Staph. epidermidis and E. Coli.

Prophylaxis

A single dose of Ceftriaxone preoperatively may reduce chances of postoperative infections.

4.2 Posology and Method of Administration

The usual adult doses is 1-2 g.o.d./b.d. Total daily dose should not exceed 4g.

In infants and young children : 20 – 80 mg/kg/day

Premature babies / Neonates : Less than 50 mg/kg/day.

4.3 Contraindications

Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients. History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

Ceftriaxone is contraindicated in:

Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)

Full-term neonates (up to 28 days of age):

- with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired
- if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt.

In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.

4.4 Special Warning and Precautions for use.

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported; however, the frequency of these events is not known .

Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full- term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium- containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation.

If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively,
infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions.

Pediatric population

Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described under Posology and Method of Administration. Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

Ceftriaxone is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy.

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. Severe cases of haemolytic anaemia, including fatalities, have been reported during Ceftriaxone treatment in both adults and children.

If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Long term treatment

During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftriaxone.

Discontinuation of therapy with ceftriaxone and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Severe renal and hepatic insufficiency

In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised.

Interference with serological testing

Interference with Coombs tests may occur, as ceftriaxone may lead to false-positive test results. Ceftriaxone can also lead to false-positive test results for galactosaemia. Non-enzymatic methods for the glucose determination in urine may false- positive results. Urine glucose determination during therapy with Ceftriaxone should be done enzymatically.

Antibacterial spectrum

Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed. In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above.

Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of ceftriaxone therapy. Rarely precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of ceftriaxone treatment should be considered by the physician based on specific benefit risk assessment.

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor of Ceftriaxone-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone. In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the physician based on specific benefit risk assessment.

This medicinal product contains 3.6 mmol (or 83 mg) of sodium in a vial. This should be taken into consideration in patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

- Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous 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.
- Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with ceftriaxone.
- There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of

aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

- In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.
- There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).
- In patients treated with ceftriaxone, the Coombs' test may lead to false-positive test results.
- Likewise, non-enzymatic methods for glucose determination in urine may yield false-positive results. For this reason, glucose level determination in urine during therapy with ceftriaxone should be carried out enzymatically.
- Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.
- No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide).
- Simultaneous administration of probenecid does not reduce the elimination of ceftriaxone.

4.6 Pregnancy and Lactation

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:

Very common (≥ 1/10);

Common (≥ 1/100 - < 1/10);

Uncommon (≥ 1/1000 - < 1/100);

Rare (≥ 1/10000 - < 1/1000);

Not known (cannot be estimated from the available data);

System Organ Class	Common	Uncommon	Rare	Not Known a
Infections and infestations		Genital fungal infection	Pseudomembranous colitisb	Superinfectionb
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemiab Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivityb
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders				
Gastrointestinal	Diarrhoeab	Nausea	Bronchospasm	Pancreatitisb

disorders	Loose stools	Vomiting		Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitationb Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndromeb Toxic epidermal necrolysisb Erythema multiforme Acute generalised exanthematous Pustulosis
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positiveb Galactosaemia test false positiveb Non enzymatic methods for glucose determination false positiveb

Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with Clostridium difficile. Appropriate fluid and electrolyte management should be instituted.

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium.

Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults.

Cases of renal precipitation have been reported, primarily in children older than 3 years of age and who have been treated with either high daily doses (e.g. ≥ 80 mg/kg/day) or total doses exceeding 10 grams and who presented with other risk factors (e.g. fluid restrictions or confinement to bed). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of ceftriaxone.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

4.9 Overdose

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdose should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins,

ATC code: J01DD04.

Mechanism of action

Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

5.2 Pharmacokinetic properties

Absorption

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone, 1 g and 2 g, the plasma ceftriaxone levels are approximately, 150 and 250 mg/l respectively. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 g is about 81 mg/l and is reached in 2 - 3 hours after administration.

The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).

Biotransformation

Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.

Elimination

Plasma clearance of total ceftriaxone (bound and unbound) is 10 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 - 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

5.3 Preclinical safety data

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.

5.4 Pharmaceutical properties

5.4.1 List of excipients

No excipients are used in manufacture of BAXCEF (Ceftriaxone for Injection USP 1 g).

5.4.2 Incompatibilities

None known.

5.4.3 Shelf life

30 Months

5.4.4 Special precautions for storage

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

5.4.5 Nature and contents of container

10 ml flint USP type I glass vial is filled, plugged with GBBR plugs and sealed with dark pink flip off seal and labeled. One such vial to be packed in a mono carton along with 10ml Sterile Water for Injection with Literature.

5.4.6 Special precautions for disposal and other handling

Keep out of reach of children.

Marketing authorization holder

KILITCH DRUGS INDIA LTD

Plot no. C-301/2, M.I.D.C T.T.C, Industrial Area, Pawane, Navi Mumbai - 400 705, Maharashtra ,INDIA.

Imported and Marketed by:

GLOBAL HEALTHCARE LTD.

12, Olusoji Idowu Street, Ilupeju, Lagos, NIGERIA.

6. MARKETING AUTHORISATION NUMBER(S) :

Not Applicable

7. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Not Applicable

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