## 1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

**Enclosed**

## 1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

**1 Name of the medicinal product:**

**1.1 Product name:** Steritax – 1.5 (Ceftriaxone Sodium and Sulbactam Sodium For Injection)

**1.2 Strength:**

Each vial contains:
Sterile Ceftriaxone Sodium USP
equivalent to Ceftriaxone 1000 mg
Sterile Sulbactam Sodium USP
equivalent to Sulbactam 500 mg

**1.3 Pharmaceutical dosage form:**

Injections

**2. Qualitative and Quantitative Composition:**

**2.1 Qualitative Declaration:**

Ceftriaxone sodium: (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2- methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxyalic acid,7²-(Z)-(O-methyloxime), disodium salt, sesquaterhydrate.

Sulbactam Sodium: sodium (2S, 5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo (3.2.0) heptane-2-carboxylate 4,4-dixoide.

**2.2 Quantitative Declaration:**

Each vial contains:
Sterile Ceftriaxone Sodium USP
equivalent to Ceftriaxone 1000 mg
Sterile Sulbactam Sodium USP
equivalent to Sulbactam 500 mg

**3. Pharmaceutical Form:**

White to off white free flowing powder for injection.

**4. Clinical Particulars:**

**4.1 Therapeutic Indications:**

Ceftriaxone and Sulbactam injection is indicated for the treatment of the following infections when caused by susceptible organisms:

i. Lower respiratory tract infections
ii. Acute bacterial otitis media
iii. Skin and skin structure infections
iv. Urinary tract infections (complicated and uncomplicated)
v. Uncomplicated gonorrhea (cervical/urethral and rectal)

vi. Pelvic inflammatory disease - Ceftriaxone, like other cephalosporins, has no activity against Chlamydia trachomatis. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and C. trachomatis is one of the suspected pathogens, appropriate antichlamydial coverage should be added.
vii. Bacterial septicemia
Bone and joint Infections
viii. Intra-abdominal Infections
ix. Meningitis
x. Surgical prophylaxis

The preoperative administration of a single 1 gm dose of ceftriaxone and sulbactam injection may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (eg, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (e.g., during coronary artery bypass surgery).
Before instituting treatment with the drug, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

**4.3 Contraindications:**

Ceftriaxone and sulbactam injection is contraindicated in patients with known allergy to the penicillin or cephalosporin class of antibiotics. It is also contraindicated in patients who have shown hypersensitivity to sulbactam. It should not be given to neonates with jaundice or to those who are hypoalbuminaemic or acidotic or have other conditions such as prematurity, in which bilirubin binding is likely to be impaired.

**4.4 Special warning and precautions for use:**

Before therapy with ceftriaxone and sulbactam injection is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.
Pseudomembranous colitis has 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 diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by

Clostridium difficile is one primary cause of "antibiotic-associated" colitis. After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against C. difficile colitis.

**PRECAUTIONS**

**General**

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone is similar to that of other cephalosporins. Ceftriaxone is excreted via both biliary and renal excretion.

Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during ceftriaxone treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during

therapy. Prolonged use of ceftriaxone may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone and sulbactam injection should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium salt. The condition appears to be transient and reversible upon discontinuation of ceftriaxone and institution of conservative management. Therefore, ceftriaxone and sulbactam injection should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Cephalosporins as a class tend to be absorbed on to the surface of the red cell membranes and react with antibodies directed against the drug to produce a positive Coombs' test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

**Effects on ability to drive and use machines -** Not applicable.

**Usage in pregnancy and lactation**

There are 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.
Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when this drug is administered to a nursing woman.

**Usage in geriatrics**

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone was only minimally altered in elderly subjects; therefore dosage adjustment is not necessary for these patients with ceftriaxone dosages up to 2 gm per day.

## 4.5 Interaction with other medicinal products and other forms of interactions:

Concomitant administration of oral probencid (500mg daily) does not appear to affect the pharmacokinetics of ceftriaxone. However, higher dosages of oral probenecid (1 or 2g daily) administered concomitantly reportedly may partially block biliary secretion of ceftriaxone as well as displace the drug from plasma proteins. As a result, serum clearance of ceftriaxone may be increased by about 30% and elimination half life of ceftriaxone may be decreased by about 20%.
Probenecid reduces renal clearance of sulbactam. Prolonged serum levels of sulbactam are achieved by concomitant administration of probenecid.
In vitro studies indicate that the antibacterial acitivity of ceftriaxone and aminoglycosides (amikacin, gentamicin, tobramycin) may be additive or synergistic against some strains of Enterobacteriaceae and some strains of Pseudomonas aeruginosa. Although the clinical importance has not been determined to date, antagonism has also occurred rarely in vitro when ceftriaxone was used in combination with an aminoglycoside.
Although the clinical importance is unclear, results of an in vitro study indicate that the combination of ceftriaxone and trovafloxacin is synergistic against both penicillin-susceptible and penicillin-resistant Streptococcus pneumoniae, including some stains that also were resistant to ceftriaxone alone. There was no evidence of antagonism with the combination of ceftriaxone and trovafloxacin.
Sulbactam is potentially and/or chemically incompatible with aminoglycosides and can inactivate the drugs in vitro.
A disulfiram like reaction reportedly occurred in one patient who ingested alcohol while receiving ceftriaxone. However this effect generally has been reported only with beta lactam antibiotics that contain an N-methylthiotetrazole (NMTT) side chain (e.g. cefamandole, cefoperazone and cefotetan).

## 4.6 Pregnancy and lactation:

There are 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.
Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when this drug is administered to a nursing woman.

## 4.7 Effect on ability to drive and use machine:

Not applicable

## 4.8 Undesirable effects:

Following adverse reactions have been observed with ceftriaxone therapy:
**Local reactions:** Pain, induration, tenderness, phlebitis and injection site reaction
**Hypersensitivity:** Rash, pruritus, fever or chills.
**Hematologic:** Eosinophilia, thrombocytosis and leukopenia. Less frequently reported were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.
**Gastrointestinal:** Diarrhea. Less frequently reported were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.
**Hepatic:** elevations of SGOT or SGPT. Less frequently reported were elevations of alkaline phosphatase and bilirubin.
**Renal:** Elevations of the BUN. Less frequently reported were elevations of creatinine and the presence of casts in the urine.
Central nervous system: Headache or dizziness were reported occasionally.
**Genitourinary:** Moniliasis or vaginitis were reported occasionally.
**Miscellaneous:** Diaphoresis and flushing were reported occasionally.
Other rarely observed reactions include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the colitis, flatulence, dyspepsia, palpitations and epistaxis.
Parenteral sulbactam sodium alone is associated with few adverse effects, principally pain at the injection site and diarrhoea.

## 4.9 Overdose:

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

## 1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

### 5. Pharmacological Properties:

### 5.1 Pharmacodynamic properties:

**Ceftriaxone**
Ceftriaxone usually is bactericidal in action. The bactericidal activity of Ceftriaxone results from inhibition of cell wall synthesis.
**Sulbactam**
Sulbactam is a penicillanic acid sulphone with betalactamase inhibitory properties. It is an irreversible inhibitor of many plasmid-mediated and some chromosomal betalactamases. It can be combined with one of the many beta-lactamase labile beta-lactam antibiotics to prevent their destruction by beta-lactamases. Sulbactam can enhance the activity of cephalosporins against many resistant strains of bacteria.

**Rationale for the combination of ceftriaxone and sulbactam**

Ceftriaxone is the preferred third-generation cephalosporin for the treatment of a variety of serious infections because of its excellent efficacy in a broad range of infections and its pharmacokinetic and tolerability profile. However, of concern is the emergence and spread of resistance to ceftriaxone among gram-negative pathogens due to beta lactamase enzymes. Sulbactam, a beta lactamase inhibitor
when combined with ceftriaxone, inhibits the beta lactamase degradation of ceftriaxone and restores the activity of ceftriaxone against resistant strains of bacteria. The combination of ceftriaxone and sulbactam thus offers a broader coverage than ceftriaxone.

**MICROBIOLOGY**
**Ceftriaxone**
Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases of gram-negative and positive bacteria.
**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 and Serratia marcescens.
Ceftriaxone is also active against many strains of Pseudomonas aeruginosa.
NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, eg, penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone.
**Gram-positive aerobes:** Staphylococcus aureus (including penicillinase-producing strains), Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, Viridans group streptococci

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., Enterococcus (Streptococcus) faecalis, are resistant.
**Anaerobes:** Bacteroides fragilis, Clostridium species, Peptostreptococcus species
NOTE: Most strains of C. difficile are resistant.
Ceftriaxone also demonstrates in vitro activity against most strains of the following microorganisms, although the clinical significance is unknown:

**Gram-negative aerobes: -** Citrobacter diversus, Citrobacter freundii, Providencia species (including Providencia rettgeri), Salmonella species (including S. typhi) and Shigella species
**Gram-positive aerobes:** Streptococcus agalactiae
**Anaerobes:** Bacteroides bivius, Bacteroides melaninogenicus
**Sulbactam**
Sulbactam itself exhibits a moderate antibacterial activity that is related to its affinity for penicillin binding proteins of various bacterial strains. Its only notable activity is against N. gonorrhoeae, N. meningitidis and Acinetobacter baumanii.

**5.2 Pharmacokinetic properties:**

**Ceftriaxone**
Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours postdosing.
Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds.
Over a 0.15 to 3 gm dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8 to 8.7 hours; apparent volume of distribution from 5.78 to 13.5 L; plasma clearance from 0.58 to 1.45 L/hour; and renal clearance from 0.32 to 0.73 L/hour. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decrease from a value of 95% bound at plasma concentrations of <25 µg/mL to a value of 85% bound at 300 µg/mL.
Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced, suggesting that plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.
**Sulbactam**
After IM administration of 0.5 g sulbactam the mean peak serum concentration of 13g/mL is attained in 30 minutes. Bioavailability of sulbactam after IM administration is same as after IV dosage. Sulbactam is widely distributed into the tissues. Mean serum half life of sulbactam is approximately 1 hour. Approximately 75 to 85% of sulbactam is excreted unchanged in the urine during the first 8 hours after administration. About 38% of sulbactam is reversibly bound to human serum protein.

## 1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

**5.3 Preclinical safety data:**

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**6. Pharmaceutical Particulars:**

**6.1 List of excipients:**

None

**6.2 Incompatibilities:**

No incompatibilities are known

**6.3 Shelf – life:**

24 months

**6.4 Special precautions for storage:**

Store below 30°C in a dry place, away from light.

**6.5 Nature and contents of container:**

Vial containing dry powder of 1000 mg / 500 mg of Ceftriaxone sodium USP/Sulbactam sodium USP in a carton along with leaflet.

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**6.6 Special precautions for disposal:**

After treatment the remaining tablets should be discarded or returned to the Pharmacist.

**7. REGISTRANT:**

| | | |
|---|---|---|
| Name | : | Ipca Laboratories Limited |
| Business Address | : | 48, Kandivli Industrial Estate<br>Kandivli (west), Mumbai – 400 067 |
| Postal Address | : | same as above |
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## 1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

**8. Manufacturer:**

| | | |
|---|---|---|
| Name | : | Ipca Laboratories Limited |
| Business Address | : | C-6, SARA Industrial Area,<br>Chakrata Road, Rampur,<br>Dehradun- 248197 Uttarakhand India. |
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**9. Date of revision of the text:**

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