1.3 PRODUCT INFORMATION

1.3.1 Summary of Product characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT
Ceftriaxone and Sulbactam for Injection 1 gm/500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains: Sterile Ceftriaxone Sodium USP equivalent to Ceftriaxone 1000mg and Sulbactam Sodium USP equivalent to Sulbactam 500mg

3. PHARMACEUTICAL FORM
A white or almost white powder filled in transparent glass vial.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
• 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

4.2 Posology and method of administration
Ceftriaxone for injection may be administered intravenously or intramuscularly.
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone for injection 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 for injection is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone for injection must not be administered simultaneously with calciumcontaining IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Ceftriaxone for injection and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

There have been no reports of an interaction between Ceftriaxone and oral calcium-containing products or interaction between intramuscular Ceftriaxone and calcium-containing products (IV or oral).
NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for injection. Ceftriaxone for injection is contraindicated in premature neonates.

Ceftriaxone for injection is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because

of the risk of precipitation of ceftriaxone- calcium.

Intravenous doses should be given over 60 minutes in neonates to reduce the risk of bilirubin encephalopathy.

PEDIATRIC PATIENTS: For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses every 12 hours). The total daily dose should not exceed 2 grams.

For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended.

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

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

ADULTS: The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because Ceftriaxone sodium has no activity against this organism.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended.

Generally, Ceftriaxone for injection 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 infections, 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 or hepatic function.

The dosages recommended for adults require no modification in elderly patients, up to 2 gm per day, provided there is no severe renal and hepatic impairment.

4.3 Contraindications

Hypersensitivity

Ceftriaxone for injection is contraindicated in patients with known hypersensitivity to Ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam antibacterial agents may be at greater risk of hypersensitivity to Ceftriaxone.

Neonates

Premature neonates: Ceftriaxone for injection is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).

Hyperbilirubinemic neonates: Hyperbilirubinemic neonates should not be treated with Ceftriaxone for injection. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients. **Neonates Requiring Calcium Containing IV Solutions**

Ceftriaxone for injection is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium.Cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Ceftriaxone for injection and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Ceftriaxone for injection and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line.

There have been no similar reports in patients other than neonates.

Lidocaine

Intravenous administration of Ceftriaxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with Ceftriaxone for intramuscular injection, exclude all contraindications to lidocaine. Refer to the prescribing information of lidocaine.

4.4 Special warnings and precautions for use

WARNINGS

Hypersensitivity Reactions

Before therapy with for injection is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins and other beta-lactam agents or other drugs. This product should be given cautiously to penicillin and other beta-lactam agentsensitive patients. Antibacterial drugs 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. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions (i.e., anaphylaxis) have been reported. In case of severe hypersensitivity reactions, treatment with

Ceftriaxone & Sulbactam must be discontinued immediately and adequate emergency measures must be initiated.

Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone for injection 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 for injection is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone for injection 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 for injection 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.

***Clostridium difficile* - Associated Diarrhea**

Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including Ceftriaxone for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Hemolytic Anemia

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone for injection. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on Ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and Ceftriaxone stopped until the etiology is determined.

PRECAUTIONS

Development of Drug-resistant Bacteria

Prescribing for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Prolonged use of Ceftriaxone for injection may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Patients with Renal or Hepatic Impairment

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone for injection are administered.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the Ceftriaxone for injection dosage should not exceed 2 gm daily. Ceftriaxone is not removed by peritoneal- or hemodialysis. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

Effect on Prothrombin Time

Alterations in prothrombin times have occurred in patients treated with for injection. Monitor prothrombin time during Ceftriaxone & Sulbactam for injection treatment in patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition). Vitamin K administration (10mg weekly) may be necessary if

the prothrombin time is prolonged before or during therapy. Concomitant use of Ceftriaxone & Sulbactam with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjustedaccordingly, both during and after treatment with Ceftriaxone & Sulbactam.

Gallbladder Pseudolithiasis

Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving Ceftriaxone & Sulbactam for injection. These precipitates 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 probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of gallbladder disease. The condition appears to be reversible upon discontinuation of Ceftriaxone & Sulbactam sodium and institution of conservative management. Discontinue Ceftriaxone & Sulbactam sodium in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

Urolithiasis and Post-Renal Acute Renal Failure

Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving Ceftriaxone & Sulbactam for injection and may be detected as sonographic abnormalities. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of urolithiasis, and ureteral obstruction and post-renal acute renal failure. The condition appears to be reversible upon discontinuation of Ceftriaxone & Sulbactam sodium and institution of appropriate management. Ensure adequate hydration in patients receiving Ceftriaxone & Sulbactam for injection. Discontinue Ceftriaxone & Sulbactam for injection in patients who develop signs and symptoms suggestive of urolithiasis, oliguria or renal failure and/or the sonographic findings described above.

Pancreatitis

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported in patients treated with Ceftriaxone & Sulbactam for injection. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of Ceftriaxone & Sulbactam for injection related biliary precipitation cannot be ruled out.

Information for Patients

- Patients should be counseled that antibacterial drugs including Ceftriaxone & Sulbactam for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., common cold).
- When Ceftriaxone & Sulbactam for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Ceftriaxone & Sulbactam for injection or other antibacterial drugs in the future.
- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Pediatric Use

Safety and effectiveness of Ceftriaxone & Sulbactam for injection in neonates, infants and pediatric patients have been established for the dosages described in the **DOSAGE AND ADMINISTRATION** section. *In vitro* studies have shown that Ceftriaxone & Sulbactam, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone & Sulbactam for injection should not be administered to hyperbilirubinemic neonates, especially prematures.

Geriatric Use

Of the total number of subjects in clinical studies of Ceftriaxone & Sulbactam for injection, 32% were 60 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of Ceftriaxone & Sulbactam were only minimally altered in geriatric patients compared to healthy adult subjects and dosage adjustments are not necessary for geriatric patients with Ceftriaxone & Sulbactam dosages up to 2 grams per day provided there is no severe renal and hepatic impairment.

Influence on Diagnostic Tests

In patients treated with Ceftriaxone & Sulbactam for injection the Coombs' test may become positive. Ceftriaxone & Sulbactam for injection, like other antibacterial drugs, may result in positive test results for galactosemia.

Nonenzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Ceftriaxone & Sulbactam for injection should be done enzymatically.

The presence of Ceftriaxone & Sulbactam may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

4.5 Interaction 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 Rocephin vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxonecalcium
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 calciumcontaining infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calciumcontaining
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.
Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia.
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.
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

Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed 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.
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.
Nonteratogenic Effects: In rats, in the Segment I and Segment III (perinatal and postnatal) studies with intravenously administered Ceftriaxone & Sulbactam, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

Nursing Mothers

Low concentrations of Ceftriaxone & Sulbactam are excreted in human milk. Caution should be exercised when Ceftriaxone & Sulbactam for injection is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Ceftriaxone & Sulbactam for injection is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Ceftriaxone & Sulbactam for injection therapy or of uncertain etiology, were observed:
LOCAL REACTIONS - pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration. The incidence of warmth, tightness or induration was 17% (3/17) after IM administration of 350 mg/mL and 5% (1/20) after IM administration of 250 mg/mL.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS-injection site pain (0.6%).
HYPERSENSITIVITY - rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.
INFECTIONS AND INFESTATIONS - genital fungal infection (0.1%).

HEMATOLOGIC - eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.
BLOOD AND LYMPHATIC DISORDERS - granulocytopenia (0.9%), coagulopathy (0.4%).
GASTROINTESTINAL - diarrhea /loose stools (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.

HEPATIC - elevations of aspartate aminotransferase (AST) (3.1%) or alanine aminotransferase (ALT) (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.
RENAL - elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.
CENTRAL NERVOUS SYSTEM - headache or dizziness were reported occasionally (<1%).
GENITOURINARY - moniliasis or vaginitis were reported occasionally (<1%).
MISCELLANEOUS - diaphoresis and flushing were reported occasionally (<1%).
INVESTIGATIONS - blood creatinine increased (0.6%).
Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General Properties
ATC classification: J01DD63

Mode of action
Ceftriaxone & Sulbactam is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.
Ceftriaxone & Sulbactam has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.
Mechanism of resistance
Resistance to Ceftriaxone & Sulbactam is primarily through hydrolysis by beta- lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.
Interaction with Other Antimicrobials In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and
Ceftriaxone & Sulbactam.
Ceftriaxone & Sulbactam has been shown to be active against most isolates of the following bacteria, both *in*

vitro and in clinical infections as described in the INDICATIONS AND USAGE section:
- Gram-negative bacteria
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens
- Gram-positive bacteria
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci
- Anaerobic bacteria
Bacteroides fragilis
Clostridium species
Peptostreptococcus species
The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the
following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the
susceptible breakpoint for Ceftriaxone & Sulbactam. However, the efficacy of Ceftriaxone & Sulbactam in treating clinical infections due to these microorganisms has not been established in adequate and wellcontrolled clinical trials.
- Gram-negative bacteria
Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species (including *Salmonella typhi*)
Shigella species
- Gram-positive bacteria
Streptococcus agalactiae
- Anaerobic bacteria
Porphyromonas (*Bacteroides*) *melaninogenicus*
Prevotella (*Bacteroides*) *bivius*

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test

results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method 1,3. The MIC values should be interpreted according to criteria provided in Table 5.

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method 2,3. This procedure uses paper disks impregnated with 30 mcg Ceftriaxone & Sulbactam to test the susceptibility of microorganisms to Ceftriaxone & Sulbactam. The disk diffusion interpretive criteria are provided in Table 5.

Anaerobic techniques

For anaerobic bacteria, the susceptibility to Ceftriaxone & Sulbactam as MICs can be determined by a standardized agar test method 3,4. The MIC values obtained should be interpreted according to the criteria provided in Table 5.

Pathogen	Minimum Inhibitory Concentrations (mcg.ml)			Disk Diffusion Zone Diameters (mm)		
	(S) Susceptible	(I) Intermediate	(R) Resistant	(S) Susceptible	(I) Intermediate	(R) Resistant
Enterobacteriaceae[a]	≤1	2	≥4	≥23	20 to 22	≤19
Haemophilus influenzae[b, c]	≤2	-	-	≥26	-	-
Neisseria gonorrhoeae[c]	≤0.25	-	-	≥35	-	-
Neisseria meningitidis[c]	≤0.12	-	-	≥34	-	-
Streptococcus	≤0.5	1	≥2	-	-	-

pneumoniae[d] meningitis isolates						
Streptococcus pneumoniae [d] non-meningitis isolates	≤1	2	≥4	-	-	-
Streptococcus species betahemolytic group[c]	≤0.5	-	-	≥24	-	-
Viridans group streptococci	≤1	2	≥4	≥27	25 to 26	≥24
Anaerobic bacteria (agar method)	≤1	2	≥4	-	-	-

a Susceptibility interpretive criteria for *Enterobacteriaceae* are based on a dose of 1 gram IV q 24h. For isolate
s with intermediate susceptibility, use a dose of 2 grams IV q 24h in patients with normal renal function.
b For *Haemophilus influenzae,* susceptibility interpretive criteria are based on a dose of 2 grams IV every 24 h
ours in patients with normal renal function.
c The current absence of data on resistant isolates precludes defining any category other than 'Susceptible'. If
isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additi
onal testing.
d Disc diffusion interpretive criteria for Ceftriaxone & Sulbactam discs against *Streptococcus pneumoniae* ar e not available, however, isolates of pneumococci with oxacillin zone diameters of ≥20 mm are susceptible (MIC ≤0.06 mcg/mL) to penicillin and can be considered susceptible to Ceftriaxone & Sulbactam. *Streptococcus pneumoniae* isolates should not be reported as penicillin Ceftriaxone & Sulbactam resistant or intermediate based solely on an oxacillin zone diameter of ≤19 mm. The Ceftriaxone & Sulbactam MIC should be determined for those isolates with oxacillin zone diameters ≤19 mm.

Susceptibility of staphylococci to Ceftriaxone & Sulbactam may be deduced from testing only penicillin and either cefoxitin or oxacillin.
A report of *Susceptible* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection. A report of *Intermediate* indicates that the result should be considered equivocal, and if the microorganism is

not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test1,2,3,4. Standard Ceftriaxone & Sulbactam powder should provide the following range of MIC values noted in Table 6. For the diffusion technique using the 30 mcg disk, the criteria in Table 6 should be achieved.

QC Strain	**Minimum Inhibitory Concentrations (mcg/mL)**	**Disk Diffusion Zone diameters (mm)**
Escherichia coli ATCC 25922	0.03 to 0.12	29 to 35
Staphylococcus aureus ATCC 25923	-----	22 to 28
Staphylococcus aureus ATCC 29213	1 to 8	-----
Haemophilus influenzae ATCC 49247	0.06 to 0.25	31 to 39
Neisseria gonorrhoeae ATCC 49226	0.004 to 0.015	39 to 51
Pseudomonas aeruginosa ATCC 27853	8 to 64	17 to 23
Streptococcus pneumoniae ATCC 49619	0.03 to 0.12	30 to 35
Bacteroides fragilis ATCC 25285 (agar method)	32 to 128	----
Bacteroides thetaiotaomicron ATCC 29741 (agar method)	64 to 256	-----

5.2 Pharmacokinetic properties

Average plasma concentrations of Ceftriaxone & Sulbactam following a single 30 minute intravenous (IV)infusion of a 0.5, 1 or 2 gm dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL or 350 mg/mL concentrations) or 1 gm dose in healthy subjects are presented in Table 1.

Dose/Route	Average Plasma Concentrations(mcg/mL)								
	0.5 hr	**1hr**	**2hr**	**4hr**	**6hr**	**8hr**	**12hr**	**16hr**	**24hr**
0.5 gm IV*	82	59	48	37	29	23	15	10	5
0.5 gm IM									
250mg/mL	22	33	38	35	30	26	16	ND	5
0.5gm IM									
350 mg/mL	20	32	38	34	31	24	16	ND	5
1 gm IV*	151	111	88	67	53	43	28	18	9
1gm IM	40	68	76	68	56	44	29	ND	ND
2 gm IV*	257	192	154	117	89	74	46	31	15

*IV doses were infused at a constant rate over 30 minutes.
ND = Not determined.

Ceftriaxone & Sulbactam was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose. Multiple IV or IM doses ranging from 0.5 to 2 gm at 12 to 24 hour intervals resulted in 15% to 36% accumulation of Ceftriaxone & Sulbactam above single dose values.

Ceftriaxone & Sulbactam concentrations in urine are shown in Table 2.

Dose/Route	Average Urinary Concentrations (mcg/mL)					
	0 to 2 hr	**2 to 4 hr**	**4 to 8 hr**	**8 to 12 hr**	**12 to 24 hr**	**24 to 48 hr**
0.5 gm IV	526	366	142	87	70	15
0.5gm IM	115	425	308	127	96	28
1gm IV	995	855	293	147	132	32
1gm IM	504	628	418	237	ND	ND
2gm IV	2692	1976	757	274	198	40

ND = Not determined

Thirty-three percent to 67% of a Ceftriaxone & Sulbactam 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. After a 1 gm IV dose, average concentrations of Ceftriaxone & Sulbactam, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, 78.2 mcg/gm in the gallbladder wall and 62.1 mcg/mL in the concurrent plasma.

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 & Sulbactam is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 mcg/mL to a value of 85% bound at 300 mcg/mL. Ceftriaxone & Sulbactam crosses the blood placenta barrier.

The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in pediatric patients suffering from bacterial meningitis are shown in Table 3. Ceftriaxone & Sulbactam penetrated the inflamed meninges of infants and pediatric patients; CSF concentrations after a 50 mg/kg IV dose and after a 75 mg/kg IV dose are also shown in Table 3.

	50 mg/Kg IV	75 mg/Kg IV
Maximum Plasma Concentrations (mcg/mL)	216	275

Elimination Half-life (hr)	4.6	4.3
Plasma Clearance (mL/hr/kg)	49	60
Volume of Distribution (mL/kg)	338	373
CSF Concentration-inflamed meninges (mcg/mL)	5.6	6.4
Range (mcg/mL)	1.3 to 18.5	1.3 to 44
Time after dose (hr)	3.7(±1.6)	3.3(±1.4)

Compared to that in healthy adult subjects, the pharmacokinetics of Ceftriaxone & Sulbactam were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (Table 4); therefore, dosage adjustments are not necessary for these patients with Ceftriaxone & Sulbactam dosages up to 2 gm per day. Ceftriaxone & Sulbactam was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of Ceftriaxone & Sulbactam was markedly reduced.

Subject Group	**Elimination Half-Life (hr)**	**Plasma Clearance (L/hr)**	**Volume of Distribution (L)**
Healthy Subjects	5.8 to 8.7	0.58 to 1.45	5.8 to 13.5
Elderly Subjects (mean age, 70.5 yr)	8.9	0.83	10.7
Patients with Renal Impairment			
Hemodialysis Patients (0 to 5mL/min)Creatinine clearance	14.7	0.65	13.7
Severe (5 to 15mL/min)	15.7	0.56	12.5
Moderate (16 to 30mL/min)	11.4	0.72	11.8
Mild (31 to 60mL/min)	12.4	0.7	13.3
Patients with Liver Disease	8.8	1.1	13.6

The elimination of Ceftriaxone & Sulbactam is not altered when Ceftriaxone & Sulbactam for injection is coadministered with probenecid.

Pharmacokinetics in the Middle Ear Fluid

In one study, total Ceftriaxone & Sulbactam concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media.

Sampling times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of Ceftriaxone & Sulbactam. Mean (± SD) Ceftriaxone & Sulbactam levels in the middle ear reached a peak of 35 (± 12)mcg/mL at 24 hours, and remained at 19 (± 7) mcg/mL at 48 hours. Based on middle ear fluid Ceftriaxone & Sulbactam concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone & Sulbactam is highly bound to plasma proteins.

The extent of binding to proteins in the middle ear fluid is unknown.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber that are additional to those included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents except 1% Lidocaine Injection BP (for intramuscular injection only). In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions. Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides, pentamidine, clindamycin phosphate and labetalol.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at temperature below 30°C. Protect from light.
Reconstituted solution should be used immediately after preparation.
KEEP OUT OF REACH OF CHILDREN

6.5. Nature and contents of container:

20 ml clear glass vial with 20 mm Grey bromo butyl rubber stopper and 20 mm aluminium white flip off seals along with 10 ml Sterile water for injection USP packed in carton with pack insert.

6.6 Special precautions for disposal and other handling

Nil

7. Marketing authorisation holder

M/S. CENTCHARLY PHARMA LTD.,
3, Angibenz Street, Abaranje, Ikotun,
Lagos,
Lagos state, Nigeria

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

Not Applicable

10. Date of Revision of the text

Not Applicable