# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Trade Name: Injxone SB
Generic Name: Ceftriaxone and Sulbactam for Injection 1.5 gm

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

No Excipients are used in this formulation.

## 3. PHARMACEUTICAL FORM

Dry Powder for Injection

## 4. Clinical particulars

### 4.1 Therapeutic indications

Ceftriaxone and Sulbactam for Injection 1.5 gm is indicated in the treatment of the following infections in adults and children including term neonates (from birth):

- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

Ceftriaxone and Sulbactam for Injection 1.5 gm may be used:
For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults

For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.

For Pre-operative prophylaxis of surgical site infections

In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection

In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

**Posology**

The dose depends on the severity, susceptibility, site and type of infection and on the age and hepato-renal function of the patient.

The doses recommended in the tables below are the generally recommended doses in these indications. In particularly severe cases, doses at the higher end of the recommended range should be considered.

Adults and children over 12 years of age (≥ 50 kg)

| Ceftriaxone Dosage* | Treatment frequency** | Indications |
|---|---|---|
| 1-2 g | Once daily | Community acquired pneumonia |
| | | Acute exacerbations of chronic obstructive pulmonary disease |
| | | Intra-abdominal infections |
| | | Complicated urinary tract infections (including pyelonephritis) |
| 2 g | Once daily | Hospital acquired pneumonia |
| | | Complicated skin and soft tissue infections |
| | | Infections of bones and joints |
| 2-4 g | Once daily | Management of neutropenic patients with fever that is suspected to be due to a bacterial infection |
| | | Bacterial endocarditis |
| | | Bacterial meningitis |

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for adults and children over 12 years of age (≥ 50 kg) that require specific dosage schedules:

**Acute otitis media**

A single intramuscular dose of ceftriaxone 1-2 g can be given. Limited data suggest that in cases where the patient is severely ill or previous therapy has failed, ceftriaxone may be effective when given as an intramuscular dose of 1-2 g daily for 3 days.

**Pre-operative prophylaxis of surgical site infections**

2 g as a single pre-operative dose.

**Gonorrhoea**

500 mg as a single intramuscular dose.

**Syphilis**

The generally recommended doses are 500 mg - 1g once daily increased to 2g once daily for neurosyphilis for 10-14days. The dose recommendations in syphilis, including neurosyphilis, are based on limited data. National or local guidance should be taken into consideration.

**Disseminated Lyme borreliosis (early and late )**

2g once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

**Paediatric population**

Neonates, infants and children 15 days to 12 years of age (< 50 kg)
For children with body weight of 50 kg or more, the usual adult dosage should be given.

| Ceftriaxone dosage* | Treatment frequency** | Indications |
|---|---|---|
| 50-80 mg/kg | Once daily | Intra-abdominal infections |
| | | Complicated urinary tract infections (including pyelonephritis) |
| | | Community acquired pneumonia |
| | | Hospital acquired pneumonia |
| 50-100 mg/kg (Max 4 g) | Once daily | Complicated skin and soft tissue infections |
| | | Infections of bones and joints |
| | | Management of neutropenic patients with fever that is suspected to be due to a bacterial infection |
| 80-100 mg/kg (max 4 g) | Once daily | Bacterial meningitis |
| 100 mg/kg (max 4 g) | Once daily | Bacterial endocarditis |

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

** Twice daily (12 hourly) administration may be considered where doses greater than 2 g daily are administered.

Indications for neonates, infants and children 15 days to 12 years (< 50 kg) that require specific dosage schedules:

**Acute otitis media**

For initial treatment of acute otitis media, a single intramuscular dose of ceftriaxone 50 mg/kg can be given. Limited data suggest that in cases where the child is severely ill or initial therapy has failed, ceftriaxone may be effective when given as an intramuscular dose of 50 mg/kg daily for 3 days.

**Pre-operative prophylaxis of surgical site infections**

50-80 mg/kg as a single pre-operative dose.

**Syphilis**

The generally recommended doses are 75-100 mg/kg (max 4 g) once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

**Disseminated Lyme borreliosis (early and late )**

50–80 mg/kg once daily for 14-21 days. The recommended treatment durations vary and national or local guidelines should be taken into consideration.

**Neonates 0-14 days**

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

* In documented bacteraemia, the higher end of the recommended dose range should be considered.

A maximum daily dose of 50 mg/kg should not be exceeded.

Indications for neonates 0-14 days that require specific dosage schedules:

**Acute otitis media**
For initial treatment of acute otitis media, a single intramuscular dose of ceftriaxone 50 mg/kg can be given.

**Pre-operative prophylaxis of surgical site infections**
20-50 mg/kg as a single pre-operative dose.

**Syphilis**
The generally recommended dose is 50 mg/kg once daily for 10-14 days. The dose recommendations in syphilis, including neurosyphilis, are based on very limited data. National or local guidance should be taken into consideration.

**Duration of therapy**
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for 48 - 72 hours after the patient has become a febrile or evidence of bacterial eradication has been achieved.

**Older people**
The dosages recommended for adults require no modification in older people provided that renal and hepatic function is satisfactory.

**Patients with hepatic impairment**
Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.

There are no study data in patients with severe hepatic impairment.

**Patients with renal impairment:**
In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance < 10 ml/min) should the ceftriaxone dosage not exceed 2 g daily.

In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Ceftriaxone is not removed by peritoneal or haemodialysis. Close clinical monitoring for safety and efficacy is advised.

**Patients with severe hepatic and renal impairment**
In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

**Method of Administration**

**Intramuscular administration**
1.5 g ceftriaxone and sulbactam for injection should be dissolved in 5ml water for injections IP. The solution should be administered by deep intramuscular injection.

Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site.

Dosages greater than 1g should be divided and injected at more than one site.

As the solvent used is lidocaine, the resulting solution should never be administered intravenously.

**Intravenous administration**
For IV injection 1.5 g ceftriaxone and sulbactam for Injection is dissolved in 9.6ml of water for injections IP. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses, greater than 2 g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

Diluents containing calcium, (e.g. Ringer's solution or 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. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery.

## 4.3 Contraindications

**Hypersensitivity**
Ceftriaxone 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 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. 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 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 and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone 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.

## 4.4 Special warnings and precautions for use

**Hypersensitivity Reactions**

Before therapy with ceftriaxone 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 agent-sensitive 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 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 bottles or to further dilute a reconstituted bottle 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 plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

**Jarisch-Herxheimer reaction (JHR)**

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after ceftriaxone treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.'

**Clostridium difficile -Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, 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.

**Paediatric population**

Safety and effectiveness of Ceftriaxone and Sulbactam for Injection 1.5 gm in neonates, infants and children have been established for the dosages described under Posology and Method of Administration (see section 4.2). Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

**Hemolytic Anemia**

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterial including ceftriaxone. 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.

**Precaution**

**Development of Drug-resistant Bacteria**

Prescribing ceftriaxone 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 may result in overgrowth of non-susceptible 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 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 dosage should not exceed 2 g 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 ceftriaxone. Monitor prothrombin time during ceftriaxone treatment in patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition). Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Concomitant use of ceftriaxone with Vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone.

**Gallbladder Pseudolithiasis**
Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving ceftriaxone. 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 sodium and institution of conservative management. Discontinue ceftriaxone 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 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 sodium and institution of appropriate management. Ensure adequate hydration in patients receiving ceftriaxone. Discontinue ceftriaxone 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. 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 related biliary precipitation cannot be ruled out.

## 4.5 Interaction with other medicinal products and other forms of interaction

Superinfections with non-susceptible microorganisms may occur. Since pseudo-membranous colitis has been reported to occur with ceftriaxone, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of Ceftriaxone & Sulbactam For Injection. Ceftriaxone, if given at higher than standard doses, may get precipitated as its calcium salt in the gall bladder, the shadows of which seen under sonography, could be mistaken for gallstones.

However, it is largely asymptomatic and the shadows disappear on discontinuation of therapy or in due course after the completion of therapy. Even in the case of symptomatic cases surgical interventions are not required, and they may be treated conservatively. Discontinuation of Ceftriaxone & Sulbactam For Injection treatment in symptomatic cases is at the discretion of the clinician. Like other cephalosporins, ceftriaxone is known to displace bilirubin from serum albumin. Hence caution needs to be exercised when considering Ceftriaxone & Sulbactam For Injection for the treatment of neonates with hyper-bilirubinemia.

In order to avoid the risk of development of bilirubin encephalopathy, use of Ceftriaxone & Sulbactam For Injection is best avoided in neonates in general and prematures in particular. During prolonged treatment with Ceftriaxone & Sulbactam For Injection, blood profile should be checked at regular intervals. Dosage adjustments are not necessary in hepatic failure. However, in patients with hepatic dysfunction and significant renal malfunction, Ceftriaxone & Sulbactam For Injection doses should not exceed an equivalent of 2g/day of Ceftriaxone. Close serum monitoring is recommended.

Extreme caution needs to be exercised in penicillin-sensitive patients. In case of serious hypersensitivity reactions, SC administration of epinephrine and other emergency measures are recommended. The allergic reaction is the indication for the interruption of Ceftriaxone & Sulbactam For Injection therapy. Ceftriaxone & Sulbactam For Injection should not be administered to neonates in general, hyperbilirubinemic neonates in particular, and to premature babies.

No impairment of renal function has been observed after concurrent administration of large doses of Ceftriaxone and potent diurectics. There is no evidence to suggest that Ceftriaxone increases renal toxicity of aminoglycosides. The elimination of Ceftriaxone is not altered by probenecid. Ceftriaxone and chloramphenicol have been shown to be antagonistic in in vitro studies. In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals. Coombs test may show false-positive results during Ceftriaxone therapy. Non-enzymatic urinary glucose estimation methods may give false-positive results.

## 4.6 Fertility, 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 (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, 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 are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a nursing 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

Ceftriaxone and Sulbactam for injection may cause dizziness. If you feel dizzy, do not drive or use any tools or machines. Talk to your doctor if you experience these symptoms.

## 4.8 Undesirable effects

Ceftriaxone and Sulbactam for Injection 1.5 gm are generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone 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.

**Postmarketing Experience:** In addition to the adverse reactions reported during clinical trials, the following adverse experiences have been reported during clinical practice in patients treated with ceftriaxone. Data are generally insufficient to allow an estimate of incidence or to establish causation.
A small number of 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 and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

**Gastrointestinal:** Pancreatitis, stomatitis and glossitis.

**Genitourinary:** Oliguria, ureteric obstruction, post-renal acute renal failure.

**Dermatologic:** Exanthema, allergic dermatitis, urticaria, edema; acute generalized exanthematous pustulosis (AGEP) and isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

**Hematological changes:** Isolated cases of agranulocytosis (< 500/mm) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

**Nervous system disorders:** Convulsion

**Other Adverse Reactions:** symptomatic precipitation of ceftriaxone calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

**Cephalosporin Class Adverse Reactions**
In addition to the adverse reactions listed above which have been observed in patients treated with ceftriaxone, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

**Adverse Reactions:** Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, a plastic anemia, hemorrhage, and superinfection.
Altered Laboratory Tests: Positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH.
Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

## 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 over dosage should be symptomatic.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Combinations of Cephalosporin and beta-lactamase inhibitors;
Mode of action: Ceftriaxone is a beta-lactam antibiotic like the penicillins with bactericidal action. Penicillin-binding proteins (PBPs) are responsible for several steps in the synthesis of the cell wall of bacteria and are found in large quantities (several hundred to several thousand molecules/bacterial cell).

Ceftriaxone inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to the specific PBPs located inside the bacterial cell wall. Ceftriaxone interferes with PBP-mediated cell wall synthesis leading to cell lysis, which is mediated by bacterial cell wall autolytic enzymes (autolysins), possibly through interference with an autolysin inhibitor.

The presence of an aminothiazolylacetyl side chain with an alpha methoxyimino group at the 7-position of the beta-lactam ring provides Ceftriaxone with enhanced antibacterial activity, particularly against the Enterobacteriaceae (e.g., E. coli, Klebsiella, Proteus, and Serratia) and increased stability against many of the betalactamases. Many strains of Pseudomonas aeruginosa are susceptible to Ceftriaxone. Other susceptible gram-negative organisms include Enterobacter, Citrobacter, Morganella, Providencia, Moraxella (Branhamella) catarrhalis, and N. meningitidis.

Ceftriaxone has exceptional activity against H. influenzae and N. gonorrhoeae and is the drug of choice for uncomplicated N. gonorrhoeae infections. It has no activity against B. fragilis but is active against many other anaerobes.

Following intramuscular administration, peak serum concentrations of Ceftriaxone and Sulbactam are seen between 15 minutes to 2 hrs. The maximum plasma conc of Ceftriaxone after a single IM dsoe of 1.0 g is about 81mg/L and is reached 2-3 hrs after

the dose while that of Sulbactam sodium is 6-24 mg/L and is reached approximately 1 hr after the dose.

Hence effective amount of beta-lactamases are destroyed by the time peak concentration of Ceftriaxone is reached allowing full potential of action of Ceftriaxone against ESBL producing Klebsiella, E coli spp. Serum concentrations have been shown to be proportional to the amount of dose administered. The area under curve (AUC) after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone sodium.

On intravenous administration Ceftriaxone sodium diffuses into the tissue fluid where if given in the recommended doses bactericidal concentrations are maintained for upto 24 hrs. Ceftriaxone is highly bound to human serum protein by about 83-90%.

**Distribution**

The volume of distribution of Ceftriaxone sodium is 7-12 L and that of Sulbactam is 18-27.6L.

Ceftriaxone sodium penetrates well into the extravascular spaces, tissue fluid and the synovial fluid of inflamed joints. The concentrations in most extracellular foci reach or exceed several times the MIC of most pathogens for at least 24 hours after a single administration.

Ceftriaxone sodium reaches therapeutically effective concentrations in patients with bacterial meningitis which are at least ten-fold the MICs of common pathogens such as, Enterobacteriaceae, H.influenzae, Meningococci, Pneumococci and Group B Streptococci. Ceftriaxone crosses placenta and is distributed in the amniotic fluid. It is also distributed in the milk.

**Metabolism and excretion:**

Ceftriaxone is not metabolised in the body and is eliminated unchanged via two pathways, urine and bile. 40-50% of parenterally administered dose is excreted into the urine within 48 hours as active drug. Thus, high concentrations are attained in urine, whatever is not excreted via kidney is excreted through bile.

Metabolism of sulbactam is less than 25%. 70-80% of Sulbactam is excreted by the kidney biliary excretion is minimal and. renal excretion is blocked by probenecid. Sulbactam and Ceftriaxone can be removed by hemodialysis.

Impaired renal function and Hepatic insufficiency: Ceftriaxone is excreted via both renal and biliary pathways therefore patients with renal failure normally require no adjustments of dose however concentration of the drug should be monitored in such patients and if there is evidence of drug accumulation then dosage adjustments should be made accordingly. Dosage adjustments are not necessary in patients with hepatic dysfunction, however in patients with
both hepatic dysfunction and significant renal failure, dosage should not exceed more than 2 gm daily with close monitoring of serum concentrations.

## 5.2 Pharmacokinetic properties

Ceftriaxone is completely absorbed with peak plasma concentrations of 40mcg/ml and 80mcg/ml at 2 to 3 hours after IM injection of 500mg and 1g dose of Ceftriaxone respectively. It follows a dose dependent non-linear pharmacokinetic because of the high (80-85%) plasma protein.

A similar AUC is observed after administration of an equivalent dose of Ceftriaxone by the IM or IV route. Widely distributed in body tissues and fluid, it crosses the inflamed as well as non-inflamed meninges and may achieve therapeutic concentrations in the CSF.
Irrespective of the dose Ceftriaxone has a half-life of between 6 to 9 hours. The half-life may be prolonged in neonates. While moderate renal impairment may not affect the halflife of Ceftriaxone appreciably, severe renal impairment does, with a longer half-life, which is further increased if accompanied with liver impairment.

Ceftriaxone at 1 - 2 g dose achieves concentrations above the MICS in the lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone; and cerebral, pleural, prostatic and synovial fluids for most of the pathogens responsible for infection, even after more than 24 hours. Urinary excretion by glomerular filtration accounts for 50-60% of the elimination. The intestinal flora has been shown to convert ceftriaxone into inactive metabolites. Biliary route accounts for 40-50% of excretion.
In case of renal impairment the biliary excretion may be the major pathway for excretion. In Infants& Children: Elimination half-life in neonates is prolonged which decreases with increasing postnatal age. In infants aged less than 8 days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 - 3 times that seen in the adults. In patients with renal failure, non-renal elimination may compensate. Sulbactam has a halflife of about 1 hour in healthy volunteers. Serum concentrations reached are proportional to the dose administered. It is predominantly eliminated through kidney in the unchanged form.

### 5.3 Preclinical safety data

Carcinogenesis
Considering the maximum duration of treatment and the class of the compound, carcinogenic studies with Ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis
Genetic toxicological tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured in vitro with Ceftriaxone. Ceftriaxone showed no potential mutagenic activity in these studies Impairment of fertility
Ceftriaxone produced no impairment in fertility when given intravenously to rats at daily doses upto 586 mg/kg/day, approximately 20 times the recommended dose of 2 gm/day.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None

### 6.2 Incompatibilities

Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides and labetalol.
Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned.
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 including total parenteral nutrition.
If treatment with a combination of another antibiotic with ceftriaxone is intended, administration should not occur in the same syringe or in the same infusion solution.

This medicinal product must not be mixed with other medicinal products except those mentioned.

**6.3 Shelf life**

24 Months

**6.4 Special precautions for storage**

Store below 30ºC in a dry place. Protect from light.

**6.5 Nature and contents of container**

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

**6.6 Special precautions for disposal and other handling**

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

**7. Marketing authorisation holder and manufacturer**

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Website: www.injectcare.com

**8. Marketing authorisation number(s):**

04359/6087/NMR/2018

**9. Date of first authorization/renewal of the authorization:**

Date of First Authorization: 20-03-2019

**10. Date of revision of the text**

19-07-2023