SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1. **Brand Name** : CEFTRISONE- 1000

1.2. **Generic Name** : Ceftriaxone for Injection USP

1.3. **Strength** : 1000 mg

1.4. **Pharmaceutical Form:** Powder for Injection

2. QUALITY AND QUANTITATIVE COMPOSITION

Each Combi pack contains:
a)1 vial of Ceftriaxone & Sulbactam for injection
Each vial contains:
Ceftriaxone Sodium USP (Sterile)
Eq. to Anhydrous Ceftriaxone ...1000mg

b)1 Ampoule of Sterile water for Injections USP
Each Ampoule contains:
Sterile Water for Injections BP ….10ml

3. PHARMACEUTICAL FORM

Visual description

White to yellowish orange crystalline powder filled in clear transparent glass vial sealed with blue Colour flip off seal.

4. CLINICAL PARTICULARS

4.1.THERAPEUTIC INDICATIONS:

- Pneumonia
- Septicaemia;
- Meningitis;
- Skin and soft tissue infections
- Infection in neutropenia patients
- Gonorrhoea
- Peri-operative prophylaxis of infections associated with surgery

4.2.POSOLOGY AND METHOD OF ADMINISTRATION

Ceftriaxone may be administered by deep intramuscular injection, or as a slow intravenous injection, after reconstitution of the solution according to the directions given below.

Intramuscular injection: 1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.
Intravenous injection: 1g ceftriaxone should be dissolved in 10ml of Water for Injections USP. The injection should be administered over at least 2-4 minutes, directly into the vein or via the

tubing of an intravenous infusion.
Adults and children 12 years and over:

Standard therapeutic dosage: 1g once daily.

Severe infections: 2-4 g daily, normally as a once daily dose.

Acute, uncomplicated gonorrhea: One dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated
Peri-operative prophylaxis: Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided doses at different injection sites), by slow intravenous injection or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.
Children under 12 years

Standard therapeutic dosage: 20-50mg/kg body-weight once daily.

Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

Reconstitution table Water for Injection (Intravenous Injection)

Vial Size	**Volume of Diluent to be added**	**Approx. available volume**	**Approx. displacement volume**
1g	10ml	10.5 ml	0.5ml

Reconstitution table 1% Lidocaine Injection BP (Intramuscular Injection)

Vial Size	**Volume of Diluent to be added**	**Approx. available volume**	**Approx. displacement volume**
1 g	3.5 ml	4.05 ml	0.55 ml

4.3. CONTRAINDICATIONS

Ceftriaxone is contraindicated in patients with known hypersensitivity to beta-lactam antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.
Hyperbilirubinaemic new-borns and preterm new-borns should not be treated with ceftriaxone.
Ceftriaxone is contraindicated in:

- premature new-borns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term new-borns (up to 28 days of age) with

- Jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired.

- If they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium.

Contraindications of lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine is used as a solvent.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The stated dosage should not be exceeded.

If lidocaine is used as a solvent ceftriaxone solution should only be used for intramuscular injection.

As with other Cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions.

Cephalosporins as a class tend to be absorbed onto 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.

Regular blood counts (haemoglobin, erythrocyte, leucocyte and platelet counts and screening for prolongation of prothrombin time) should be carried out during treatment.

Cephalosporins may cause bleeding due to hypoprothrombinaemia and should be used with caution in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and also in patients receiving prolonged cephalosporin therapy who are at increased risk of developing hypoprothrombinaemia.

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 diarrhoea 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.

An immune mediated haemolytic anaemia has been observed in patients receiving

cephalosporin class antibacterials including ceftriaxone. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.
Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of ceftriaxone. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.
Ceftriaxone should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

4.5. INTERATION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Aminoglycoside antibiotics and diuretics: No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g.furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides.
Alcohol: No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.
Antibiotics: In an in vitro study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.
Anticoagulants: As ceftriaxone has an N-methylthiotriazine side-chain, it might have the potential to cause hypoprothrombinaemia. Resulting in an increased risk of bleeding in patients treated with anticoagulants.
Oral Contraceptives: Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.
Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.
Interference with Laboratory Tests:

In patients treated with ceftriaxone, the Coombs' test may in rare cases be false-positive.

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

4.6. PREGNANCY AND LACTATION

Pregnancy:

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed. Therefore, ceftriaxone should not be used in pregnancy unless absolutely indicated.
Breastfeeding:

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

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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

4.8. UNDESIRABLE EFFECTS

Loose stools or Diarrhoea, Nausea, Vomiting, Stomatitis, Glossitis, Haemolytic Anaemia, Granulocytopenia, Leukopenia, Neutropenia, Thrombocytopenia, & Eosinophilia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

4.9. OVERDOSE

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMICS PROPERTIES

Ceftriaxone is a cephalosporin/cephamycin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. Ceftriaxone has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. Ceftriaxone works by inhibiting the mucopeptide synthesis in the bacterial cell wall. The beta-lactam moiety of Ceftriaxone binds to carboxypeptidases, endopeptidases, and transpeptidases in the bacterial cytoplasmic membrane. These enzymes are involved in cell-wall synthesis and cell division. By binding to these enzymes, Ceftriaxone results in the formation of defective cell walls and cell death.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of ceftriaxone are largely determined by its concentration-dependent binding to plasma albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentrations of 300mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg ceftriaxone in 1% Lidocaine Injection BP produces mean peak plasma concentrations of 40-70 mg/l within one hour. Bioavailability after intramuscular injection is 100%.

Ceftriaxone is eliminated mainly as unchanged drug, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10-22 ml/min. The renal clearance is 5-12 ml/min. A notable feature of ceftriaxone is its relatively long plasma elimination half-life of approximately eight hours which makes single or once daily dosage of the drug appropriate for most patients. The half-life is not significantly affected by the dose, the route of administration or by repeated administration

5.3. PRECLINICAL SAFETY DATA

There are no preclinical data.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Not applicable.

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 section 6.6

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 (see section 4.2, 4.3, 4.4 and 4.8).

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 in section 6.6.

6.3. SHELF LIFE

36 Months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

10ml Glass Moulded Vial Clear USP Type-III

6.6. SPECIAL PRECAUTION FOR DISPOSAL

1g vial - Concentrations for the intravenous injection: 100 mg/ml,
1g vial - Concentrations for the intravenous infusion: 50 mg/ml
2g vial - Concentrations for the intravenous injection or intravenous infusion: 50 mg/ml

(Please refer to section 4.2 for further information).

Reconstitution Table

Strength	Administration route	Diluent	Volume of diluent to be added (ml)	Approximate available volume (ml)	Approximate displacement volume (ml)
1g	Intravenous injection[1]	Water for injections	10ml	10.8ml	0.8ml
1g	Intramuscular injection	1% lidocaine	3.5ml	4.1ml	0.6ml
2g	Intramuscular injection[2]	1% lidocaine	7ml	8.4ml	1.4ml
2g	Intravenous injection or infusion	See list of compatible diluents below*	40ml	41.5ml #	1.5ml[#]

[1] For Intravenous injection, 1g ceftriaxone is dissolved in 10ml of Water for Injections. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.

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

[#] These approximate available volume and approximate displacement volume values are when reconstituted using Water for Injections.

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicinal product, see section 6.3.

Ceftriaxone should not be mixed in the same syringe with any drug other than 1% Lidocaine Injection BP (for intramuscular injection only).

*Ceftriaxone is compatible with several commonly used intravenous infusion fluids e.g. Sodium Chloride Intravenous Infusion BP, 5% or 10% Glucose Intravenous Infusion BP, Sodium Chloride and Glucose Intravenous Infusion BP (0.45% sodium chloride and 2.5% glucose), Dextran 6% in Glucose Intravenous Infusion BP 5%, isotonic hydroxyethylstarch 6- 10% infusions and Water for Injections.

The reconstituted solution should be clear. Do not use if particles are present.

Ceftriaxone sodium when dissolved in Water for Injections Ph Eur forms a pale yellow to amber solution. Variations in the intensity of colour of the freshly prepared solutions do not indicate a change in potency or safety.

For single use only. Discard any unused contents.

7. MARKETING AUTHORIZATION HOLDER

UNISOURCE PHARMA LIMITED
UNIT: 503-504,
5TH FLOOR HUBTOWN SOLARIS,
N.S. PHADKE MARG, ANDHERI (EAST) MUMBAI – 400 069
INDIA

Name and address of the manufacture
M/s Malik Lifesciences Pvt. Ltd.
Plot No. 16, Vardhman Industrial Estate,
Vill- Bahadarpur Saini, NH-58, Haridwar-247667, Uttarakhand,
INDIA.

8. MARKETING AUTHORIZATION NUMBER (S)

TAN 22 HM 0435

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

07th October, 2022

10. DATE OF REVISION OF THE TEXT