Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Ceftriaxone Injection IP

(Brand Name: EXTACEF®- i Injection)

2. Qualitative and Quantitative Composition

Each Combipack Contains:

Ceftriaxone Injection IP 1 g

Each Vial Contains:

Ceftriaxone Sodium IP (Sterile) Equivalent to Anhydrous Ceftriaxone ……..…. 1000 mg.

Each FFS ampoule contains:

Sterile water for injection IP …….. 10 ml.

(For reconstitution)

3. Dosage Form and Strength

Dosage Form: Injection.

Dosage Strength: Ceftriaxone 1000 mg per vial.

4. Clinical Particulars

4.1 Therapeutic Indication

EXTACEF-i injection is indicated for the treatment of the following bacterial infections when caused by susceptible organisms.

- Lower Respiratory Tract Infections (E.g., Pneumonia)
- Acute Otitis Media
- Skin and Skin Structure Infections
- Urinary Tract Infections (E.g., Cystitis, Pyelonephritis)
- Uncomplicated Gonorrhea
- Pelvic Inflammatory Disease
- Bacterial Septicemia
- Bone and Joint Infections
- Intra-Abdominal Infections
- Meningitis
- Surgical Prophylaxis
- Typhoid Fever

4.2Posology and Method of Administration

Ceftriaxone may be administered by deep intramuscular (I.M.) injection, slow intravenous (I.V.) injection, or as a slow I.V. infusion, after reconstitution with sterile water for injection.

Dosage Recommendations in Pediatric Patients

For children with bodyweight above 50 kg or age over 12 years, the usual adult dosage should be administered.

Usual Recommended Dosage: 50 to 75 mg/kg/day, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.

Treatment of Meningitis: The initial therapeutic dose should be 100 mg/kg body weight. Thereafter, daily dose of 100 mg/kg may be administered once a day or in equally divided doses every 12 hours. The total daily dose of ceftriaxone should not exceed 4 grams.

The usual duration of therapy is 7 to 14 days depending on the type and severity of infection.

Or, as prescribed by the physician.

Dosage Recommendations in Adults

Usual Recommended Dosage: 1 to 2 grams of ceftriaxone per day given once a day or in equally divided doses twice a day. The total daily dose should not exceed 4 grams.

For Uncomplicated Gonococcal Infections: A single dose of 250 mg of ceftriaxone is recommended by I.M. route.

For Preoperative Use (Surgical Prophylaxis): A single dose of 1 gram administered I.V. 30 minutes to 2 hours before surgery is recommended.

The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

Or, as prescribed by the physician.

Pharmaceutical Precautions

Ceftriaxone injection should not be mixed with other drugs in infusion bottle since compatibility has not been established.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Reconstitution and Dilution for Use

Each vial should be reconstituted with sterile water for injection IP (SWFI -supplied separately as a part of combipack). Shake well until powder gets dissolved. For I.V. infusion use, reconstituted solution may be further diluted with a compatible diluent (e.g., sterile water for injection, 0.9% sodium chloride injection, 5% or 10% dextrose solution). I.V. infusion may be administered over a period of at least 30 minutes, except in neonates where administration over 60 minutes is recommended to reduce the risk of bilirubin encephalopathy. The reconstituted solution should be

used immediately after preparation. Do not freeze. Unused portion of solution should be discarded immediately.

Incompatibility / Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for I.V. administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same I.V. administration line.

Ceftriaxone must not be administered simultaneously with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition.

4.3Contraindications

EXTACEF-i injection is contraindicated in the following:

- In patients with known hypersensitivity to ceftriaxone (cephalosporin class of antibiotics) or to any component of the formulation.
- Hyperbilirubinemic neonates (≤ 28 days): Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.
- Premature neonates: Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).
- Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing I.V. solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium.
- Intravenous administration of ceftriaxone solutions containing lidocaine is contraindicated.

4.4Special Warnings and Precautions for Use

Test Dose: Before therapy with ceftriaxone containing injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to ingredients of injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Hypersensitivity: 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. 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.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** 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*. 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 of antibacterial drugs 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.

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 nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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, and total parenteral nutrition). A cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

Urolithiasis and Post-Renal Acute Renal Failure: Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving ceftriaxone. 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 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.

Gallbladder Pseudolithiasis: Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving ceftriaxone. 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.

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.

Altered Laboratory Tests: Positive direct Coombs' test and galactosemia test, false-positive test for urinary glucose and elevated lactate dehydrogenase (LDH).

4.5Drug Interactions

Amsacrine, Vancomycin, Fluconazole, and Aminoglycosides: Ceftriaxone is incompatible with these drugs.

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.

Chloramphenicol: Caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

Vitamin K Antagonist: 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.

4.6Use in Special Populations

Pregnant Women

Ceftriaxone is Pregnancy Category B drug. Animal studies have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EXTACEF-i Injection should be used during pregnancy only if clearly needed.

Lactating Women

Low concentration of ceftriaxone is excreted in human milk. Therefore, caution should be exercised when ceftriaxone injection is administered to a nursing woman.

Pediatric Patients

Safety and effectiveness of ceftriaxone have been established in neonates, infants and pediatric patients. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Thus, ceftriaxone should not be administered to hyperbilirubinemic neonates, especially prematures. For administration of this medicine in children, please refer 'Posology and Method of Administration' section.

Geriatric Patients

Dosage adjustments are not necessary for geriatric patients with ceftriaxone dosages up to 2 grams per day provided there is no severe renal and hepatic impairment.

Renal or Hepatic Impairment Patients

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, when usual doses are administered in patients with renal failure or hepatic dysfunction, no dosage adjustments is necessary. However, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the ceftriaxone dosage should not exceed 2 gram daily.

4.7Effect on Ability to Drive and Use Machines

During treatment with ceftriaxone, undesirable effects such as dizziness, headache, and convulsions may occur, which may influence the ability to drive and use machines. If affected by such events, patients should not drive or operate machinery.

4.8Undesirable Effects

Ceftriaxone is generally well tolerated. The following adverse reactions were observed (related to ceftriaxone therapy or of uncertain etiology).

Local Reactions: Injection site pain, induration, tenderness, phlebitis, warmth, tightness.

Hypersensitivity: Rash, pruritus, fever or chills.

Infections and Infestations: Genital fungal infection.

Hematologic: Eosinophilia, thrombocytosis, leukopenia. Less frequently reported were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

Blood and Lymphatic Disorders: Granulocytopenia, coagulopathy.

Gastrointestinal: Diarrhea/loose stools, nausea, vomiting, dysgeusia, pseudomembranous colitis.

Hepatic: Elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin.

Renal: Elevations of blood urea nitrogen (BUN), creatinine and the presence of casts in the urine.

Central Nervous System: Headache, dizziness.

Genitourinary: Moniliasis, vaginitis.

Miscellaneous: Diaphoresis, flushing, increased blood creatinine.

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, decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

Post-marketing Experience

Gastrointestinal: Pancreatitis, stomatitis, 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: Isolated cases of agranulocytosis have been reported, most of them after 10 days of treatment and following total doses of 20 g or more.

Nervous System Disorders: Convulsion.

Others: Symptomatic precipitation of ceftriaxone-calcium salt in the gallbladder, kernicterus, oliguria, and anaphylactic or anaphylactoid reactions.

Adverse Reactions Reported for Cephalosporin-Class Drugs: Following adverse reactions have been reported for cephalosporin-class antibiotics:
Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, fixed drug eruption (FDE), purpura and superinfection.

4.9Overdose

In the case of overdose nausea, vomiting, diarrhea can occur. Ceftriaxone concentration cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be supportive and symptomatic according the patient's clinical presentation.

5. Pharmacological Properties

5.1 Mechanism of Action

Ceftriaxone is a third generation cephalosporin class of beta-lactam antibiotic. Ceftriaxone inhibits bacterial cell wall synthesis and produces bactericidal effect. Ceftriaxone has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

5.2Pharmacodynamic Properties

Ceftriaxone has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections:

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% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftriaxone. However, the efficacy of ceftriaxone in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled 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*

5.3Pharmacokinetic Properties

Absorption: Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 gram is about 81 mg/l and is reached in 2 to 3 hours after administration. The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone (C_{max}) levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively. An 8 to 15 % increase in C_{max} is seen on repeated administration; steady state is reached in most cases within 48 to 72 hours depending on the route of administration.

Distribution: The volume of distribution of ceftriaxone is 7 to 12 litre. Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).

Metabolism: Ceftriaxone is not metabolized systemically; but is converted to inactive metabolites by the gut flora.

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

6. Nonclinical Properties

6.1 Animal Toxicology

LD50 values after administration of ceftriaxone by intravenous route were in mice 1840 mg/kg, in rat 2240 mg/kg, and in rabbit 240 mg/kg. LD50 value reported after administration of ceftriaxone by oral route in mice and rats was >10,000 mg/kg.

In a 2-week intravenous administration study, groups of eight male Füllinsdorf rats were administered 0, 25 or 60 mg/kg/day of ceftriaxone. Body weight gain was slightly depressed by 9.2 and 20.1% in the 25 and 60 mg/kg/day groups respectively. The average weight of the thyroid glands was increased in the treated groups by 11 to 14% in comparison to the control animals. A 50% reduction in plasma bilirubin in the treated rats was reported along with a decrease in the number of leucocytes.

Genetic toxicology 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 for mutagenic activity in these studies.

Carcinogenicity studies on ceftriaxone were not conducted.

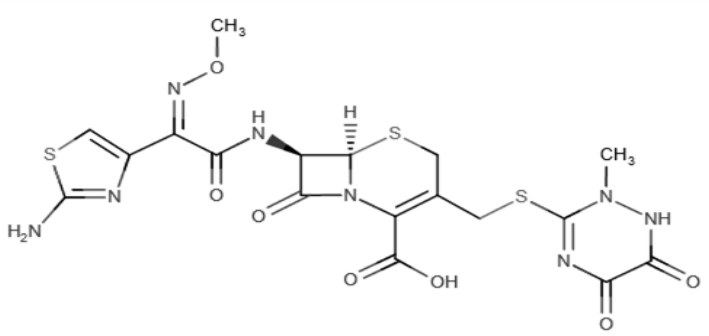
Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

7. Description

EXTACEF-i Injection is white or almost white powder filled in 10 ml clear glass vials.
Each vial contains 1000 mg of anhydrous ceftriaxone for I.M. or I.V. injection.

Ceftriaxone is a beta-lactam, third-generation cephalosporin antibiotic with bactericidal activity. Ceftriaxone sodium is white or yellowish, crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The color of ceftriaxone solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.
Molecular Weight: 554.6g/mol.
Molecular Formula: C18H18N8O7S3.
Chemical Name: (6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(2-methyl-5,6-dioxo-1H-1,2,4-triazin-3-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
Structural Formula of Ceftriaxone:



8. Pharmaceutical Particulars

8.1 Incompatibilities

Vancomycin, amsacrine, aminoglycosides, and fluconazole are incompatible with ceftriaxone in admixtures. Ceftriaxone solution for injection is incompatible with any calcium-containing product. See 'Posology and Method of Administration' section for further details.

8.2Shelf-life

24 months.
After reconstitution and/or dilution, to avoid microbiological contamination, the solution should be used immediately. Unused/remaining portion of the solution, if any, should be discarded.

8.3Packaging Information

Combipack of 1 glass vial and one FFS ampoule of 10 ml sterile water for injection in a monocarton.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patient to store medication as advised and not to expose the vial to moisture or direct light.
- Patients should be counseled that antibacterial drugs including ceftriaxone should only be used to treat bacterial infections. They do not treat viral infections (e.g., common cold).
- When ceftriaxone 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 decrease the effectiveness of therapy and increase the likelihood that bacteria will develop antimicrobial resistance.
- 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 even as late as two months after the last dose of the antibiotic. If this occurs, instruct patients to contact their physician immediately.
- Instruct patient not to freeze the reconstituted solution and use it immediately after the preparation. Unused portion of solution, if any, should be discarded.

10.Details of Manufacturer

Nitin Lifesciences Ltd.,
Rampur Road, Paonta Sahib, Dist. Sirmour,
Himachal Pradesh – 173 025, India.

11. Details of Permission or License Number with Date

DCG(I) approval date: April 1988.
Manufacturing license No. MB/05/209 dated 27/04/2006.

12. Date of Revision

February 2023.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.