For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

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

Prescribing Information

1. Generic Name

Cefixime Oral Suspension IP

(**Brand Name:** EXTACEF® Drops / EXTACEF®-P Dry Syrup / EXTACEF®-DS Dry Syrup)

2. Qualitative and Quantitative Composition

EXTACEF Drops

Each combipack contains:

A) Cefixime Oral Suspension IP
Each ml (approx. 20 drops) of reconstituted suspension contains:
Cefixime IP as Trihydrate equivalent to Anhydrous Cefixime …..……. . 50 mg.
Excipients ……..…….. q.s.

B) Sterile Water for Injections IP ……. 10 ml.

EXTACEF-P Dry Syrup

Each combipack contains:

A) Cefixime Oral Suspension IP
Each 5 ml of reconstituted suspension contains:
Cefixime IP as Trihydrate equivalent to Anhydrous Cefixime …..……. . 50 mg.
Excipients ……..…….. q.s.

B) Sterile Water for Injections IP ……. 25 ml.

EXTACEF-DS Dry Syrup

Each combipack contains:

A) Cefixime Oral Suspension IP
Each 5 ml of reconstituted suspension contains:
Cefixime IP as Trihydrate equivalent to Anhydrous Cefixime …..……. . 100 mg.
Excipients ……..…….. q.s.

B) Sterile Water for Injections IP ……. 25 ml.

3. Dosage Form and Strength

Dosage Form: Oral liquid.

Dosage Strength: Cefixime 50 mg per ml, 50 mg per 5 ml, and 100 mg per 5 ml.

4. Clinical Particulars

4.1 Therapeutic Indication

EXTACEF is indicated for the treatment of the following acute infections when caused by susceptible bacteria:

- Upper Respiratory Tract Infections (URTIs): E.g., Otitis media, pharyngitis and tonsillitis.
- Lower Respiratory Tract Infections (LRTIs): E.g., Bronchitis, pneumonia.
- Urinary Tract Infections (UTIs): E.g., Cystitis, cystourethritis, uncomplicated pyelonephritis.
- Uncomplicated Gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoae* (penicillinase-and non-penicillinase-producing isolates).
- Typhoid fever.

4.2Posology and Method of Administration

For oral administration.

Children above 6 Months:

Usual Recommended Dose: Cefixime 8 mg/kg/day administered as a single dose or in two divided doses.

Typhoid Fever: Cefixime up to 20 mg/kg/day as a single dose or in 2 divided doses.

The safety and efficacy of cefixime has not been established in children less than 6 months.

Or, as prescribed by the physician.

Adults and Children over 10 Years:

Usual Recommended Dose: Cefixime 200 to 400 mg daily according to the severity of infection, and given either as a single dose or in two divided doses.

Uncomplicated Gonorrhea: Cefixime 400 mg as single dose.

Children weighing more than 50 kg or older than 10 years should be treated with the recommended adult dose.

Or, as prescribed by the physician.

Absorption of cefixime is not significantly modified by the presence of food. Thus, EXTACEF may be taken regardless of food. The usual duration of treatment is 7 days. This may be continued for up to 14 days if required (such as in case of typhoid fever and other complicated and severe infections).

Directions for Reconstitution of Dry Syrup

Shake the bottle to loosen powder. Then, open both the containers and add water for injection (supplied separately as a part of combipack) in to the bottle to make reconstituted suspension. Close, invert and shake well. Shake the bottle well before each dose.

4.3Contraindications

EXTACEF is contraindicated in patients with known hypersensitivity to cefixime or to cephalosporin/beta-lactam antibiotics or to any component of the formulation.

4.4Special Warnings and Precautions for Use

Hypersensitivity to penicillins: As with other cephalosporins, cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with EXTACEF, the drug should be discontinued and the patient treated with appropriate agents if necessary.

Severe cutaneous adverse reactions: Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken. EXTACEF should be given with caution to patients who have shown hypersensitivity to other drugs.

Hemolytic anemia: Drug-induced hemolytic anemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of hemolytic anemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) – associated hemolytic anemia has also been reported.

Acute renal failure: As with other cephalosporins, cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Antibiotic-associated diarrhoea: Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics.

Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

4.5Drug Interactions

Anticoagulants: As with other cephalosporins, increases in prothrombin time have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy. Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g., warfarin potassium. Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

Other forms of interaction: A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.
A false positive direct Coombs test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs test may be due to the drug.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and has revealed no evidence of impaired fertility or harm to the fetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect. There are no adequate and well-controlled studies in pregnant women. Thus, EXTACEF can be administered to pregnant women only if clearly needed and under medical supervision.

Lactating Women

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with cefixime.

Paediatric Patients

Safety of cefixime in premature or newborn infants has not been established. Use of cefixime under 6 months of age is not recommended. For dosage, please refer ‘Posology and Method of Administration’ section.

Geriatric Patients

Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment.

Renal Impairment Patients

EXTACEF may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min or patients on peritoneal dialysis or haemodialysis, it is recommended that a dose of 200 mg once daily should not be exceeded.

4.7Effect on Ability to Drive and Use Machines

In the case of side effects such as encephalopathy (which may include convulsion, confusion, impairment of consciousness, movement disorders), the patient should not operate machines or drive a vehicle.

4.8Undesirable Effects

Clinical Trials Experience

The most commonly reported adverse reactions were gastrointestinal events. Individual adverse reactions included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%.

Post-Marketing Experience

Acute Generalized Exanthematous Pustulosis (AGEP) as an adverse drug reaction reported with the use of cefixime.

The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%).

Gastrointestinal: Several cases of documented pseudomembranous colitis were identified in clinical trials. The onset of symptoms may occur during or after therapy.

Dermatologic/Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, serum sickness-like reactions, and acute generalized exanthematous pustulosis (AGEP) have been reported.

Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase; hepatitis, jaundice.

Renal: Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System: Headaches, dizziness, seizures.

Hematologic System: Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.

Other Adverse Reactions: Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

Abnormal Laboratory Tests: Hyperbilirubinemia.

Adverse Reactions Reported for Cephalosporin-Class Drugs: Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, fixed drug eruption (FDE) and colitis. 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.

4.9Overdose

There is no experience regarding overdose with cefixime. Cefixime is not removed from the circulation in significant quantities by dialysis. No specific antidote exists. General supportive measures are recommended.

5. Pharmacological Properties

5.1 Mechanism of Action

Cefixime is an oral third generation cephalosporin which has marked *in vitro* bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.

Cefixime inhibits bacterial cell wall synthesis during cell multiplication and produces bactericidal action.

5.2Pharmacodynamic Properties

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

Gram-positive bacteria

- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Gram-negative bacteria

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Escherichia coli*
- *Proteus mirabilis*
- *Neisseria gonorrhoeae*

The following *in vitro* data are available, but their clinical significance is unknown. Cefixime exhibits *in vitro* MICs of 1 mcg/ml or less against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of cefixime in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

- *Streptococcus agalactiae*

Gram-negative bacteria

- *Haemophilus parainfluenzae*
- *Proteus vulgaris*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Pasteurella multocida*
- *Providencia species*
- *Salmonella species*
- *Shigella species*
- *Citrobacter amalonaticus*
- *Citrobacter diversus*
- *Serratia marcescens*

5.3Pharmacokinetic Properties

Absorption and Distribution: The absolute oral bioavailability of cefixime is in the range of 20 to 55%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals. The average serum level is approximately 1 μg/ml. Little or no accumulation of cefixime occurs following multiple dosing. Serum protein binding is concentration-independent with a bound fraction of approximately 65%. Cefixime is almost exclusively bound to the albumin fraction. Protein binding of cefixime is only

concentration-dependent in human serum at very high concentrations which are not seen following clinical dosing.

Metabolism and Excretion: There is no evidence of metabolism of cefixime *in vivo*. Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours, but may range up to 9 hours in some volunteers.

6. Nonclinical Properties

6.1 Animal Toxicology

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage in vitro and did not exhibit clastogenic potential in vivo in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

7. Description

EXTACEF Drops is White to off white free flowing powder filled in amber colour glass bottle.

EXTACEF-P Dry Syrup is Off white free flowing powder filled in amber colour glass bottle.

EXTACEF-DS Dry Syrup is Off white free flowing powder filled in amber colour glass bottle.

EXTACEF Drops contain 50 mg of cefixime per ml; EXTACEF-P Dry Syrup contains 50 mg of cefixime per 5 ml; EXTACEF-DS Dry Syrup contains 100 mg of cefixime per 5 ml. These preparations are administers orally, especially in children.

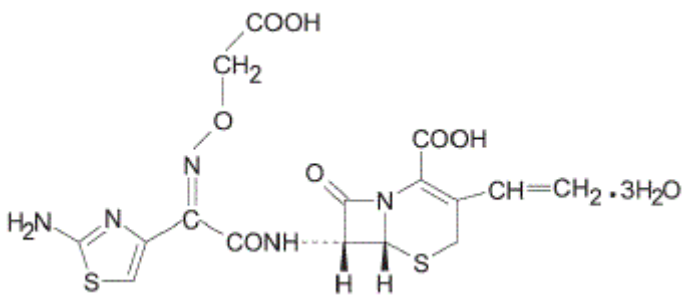
Cefixime is a broad-spectrum, third-generation cephalosporin class of beta-lactam antibiotic.

Molecular Weight: 507.5 g/mol.

Molecular Formula: $C_{16}H_{21}N_5O_{10}S_2$.

Chemical Name: (6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(carboxymethoxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; trihydrate.

Structural Formula:



Inactive ingredients (excipients) of EXTACEF Drops contain Colloidal Silicon Dioxide, Flavour Capsoroma Strawberry, Sucrose, Sodium CMC, Sodium Benzoate, Saccharine Sodium, Talcum & Magnesium Stearate.

Inactive ingredients (excipients) of EXTACEF-P Dry Syrup contain Colloidal Silicon Dioxide, Flavour Capsoroma Strawberry, Sucrose, Sodium CMC, Sodium Benzoate, Saccharine Sodium.

Inactive ingredients (excipients) of EXTACEF-DS Dry Syrup contain Colloidal Silicon Dioxide, Aspartame, Flavour Capsoroma Strawberry, Sucrose, Methyl Paraben, Sodium CMC, Sodium Citrate, Citirc Acid (Anhydrous) & Propyl Paraben.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 Months

8.3Packaging Information

EXTACEF Drops: Combipack of 10 ml amber colour glass bottle with calibrated dropper and one FFS ampoule of 10 ml sterile water for reconstitution.
EXTACEF-P Dry Syrup: Combipack of 30 ml amber colour glass bottle with measuring cup and one FFS ampoule of 25 ml sterile water for reconstitution.
EXTACEF-DS Dry Syrup: Combipack of 30 ml amber colour glass bottle with measuring cup and one FFS ampoule of 25 ml sterile water for reconstitution.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.
Store reconstituted suspension in a refrigerator between 2°C to 8°C, and use the same within 7 days.

9. Patient Counseling Information

Administration Instructions

- Patients/parents/care givers should be counseled that antibacterial drugs should only be used to treat bacterial infections. Not to use this medicine to treat infections caused by viruses.
- Patients/parents 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 the treatment and increase the likelihood that bacteria will develop resistance to antibiotic.

- Advise patients/parents that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued.
- Sometimes after starting treatment with antibacterial drugs, 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 antibacterial drug. If this occurs, patients/parents should contact their physician as soon as possible.

10. Details of Manufacturer

Malik Lifesciences Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceutical Ltd.)
Plot No. – 16, Vardhman Industrial Estate, N.H. 58,
Haridwar – 247 667, Uttarakhand.

11. Details of Permission or License Number with Date

EXTACEF Drops: Mfg. Lic No. : 48/UA/SC/P- 2013.Date of FDA product permission 28/02/2018

EXTACEF-P Dry Syrup: Mfg. Lic No. : 48/UA/SC/P- 2013.Date of FDA product permission 03/06/2015

EXTACEF-DS Dry Syrup: Mfg. Lic No. : 48/UA/SC/P- 2013. Date of FDA product permission 03/06/2015

12. Date of Revision

September 2022.