For the use of a Registered Medical Practitioner/Hospital/ Laboratory Only.

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Cefixime for Oral Suspension IP

CEFXIATIM® 100 DS

1. GENERIC NAME
Cefixime for Oral Suspension IP

FOR PAEDIATRIC USE ONLY.
(Combipack with Sterile Water for Reconstitution)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each combipack contains:
(A) Cefixime for Oral Suspension IP
Each 5 ml of reconstituted
suspension contains:
Cefixime IP as Trihydrate
Equivalent to Anhydrous
Cefixime.....100 mg
Excipients.....q.s.
Colours: Quinoline Yellow WS & Quinoline Yellow Lake
Flavour: Mango
(B) 1 Ampoule of Sterile Water for Reconstitution - 30 ml

3. DOSAGE FORM
Powder for Oral Suspension

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATION
For the treatment of enteric (typhoid) fever.
4.2 Posology and method of administration
Posology
Children: The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hourly or as directed by the Physician.
Adults: Once Cefixime is reconstituted, the recommended dose of the suspension is 400 mg daily. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended or as directed by the Physician.
Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.
The duration of treatment is dependent on the course of the infection. Generally, the duration of treatment with antibiotics is 7-10 days. It should be noted that streptococcal infections require a minimum therapy of 10 days in order to avoid secondary illnesses.
The safety and efficacy in children aged less than 6 months has not been established.
Patients with impaired renal function: Cefixime 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. There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended.
Method of administration: For oral administration only.
After reconstitution the suspension may be kept for 14 days either at room temperature, or under refrigeration, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days.
The absorption of cefixime is not significantly affected by the presence of food. Hence it can be administered with or without food.

4.3 CONTRAINDICATIONS
Cefixime is contraindicated in patients with known allergy to cefixime or other cephalosporins.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hypersensitivity Reactions
Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime. Before therapy with Cefixime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefixime occurs, discontinue the drug.
Clostridium difficile-Associated Diarrhea
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefixime, 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 isolates 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 antibacterial drug 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 antibacterial drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
Dose Adjustment in Renal Impairment
The dose of Cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully.
Coagulation Effects
Cephalosporins, including Cefixime, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.
Development of Drug-Resistant Bacteria
Prescribing Cefixime (cefixime) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.5 DRUG INTERACTION
Carbamazepine
Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.
Warfarin and Anticoagulants
Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.
Drug/Laboratory Test Interactions
A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

4.6 USE IN SPECIAL POPULATION
Pregnancy
Pregnancy Category B Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Labor and Delivery
Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.
Nursing Mothers
It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.
Pediatric Use Safety and effectiveness of cefixime in children aged less than six months old have not been established. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.
Geriatric Use
Clinical studies did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. A pharmacokinetic study in the elderly detected differences in pharmacokinetic parameters. These differences were small and do not indicate a need for dosage adjustment of the drug in the elderly.
Renal Impairment
The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully.

4.7 EFFECTS 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.

4.8 UNDESIRABLE EFFECTS
Fixed drug eruption (FDE) has been reported with cephalosporin class formulations
Acute Generalized Exanthematous Pustulosis (AGEP) / Mouth Ulceration
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most commonly seen adverse reactions in U.S. trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the twice daily or the once daily regimen. Five percent (5%) of patients in the U.S. clinical trials discontinued therapy because of drug-related adverse reactions. Individual adverse reactions included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.
Post-marketing Experience
The following adverse reactions have been reported following the post-approval 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 pseudomembranous colitis symptoms may occur during or after therapy.
Hypersensitivity Reactions
Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions 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.
Hemic and Lymphatic System
Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.
Abnormal Laboratory Tests
Hyperbilirubinemia
Other Adverse Reactions
Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.
Adverse Reactions Reported for Cephalosporin-class Drugs
Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, 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.

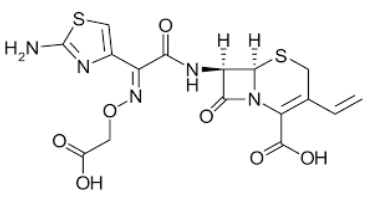
4.9 Overdose
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

5. PHARMACOLOGICAL PROPERTIES
5.1 MECHANISM OF ACTION
Cefixime is a semisynthetic cephalosporin antibacterial drug
5.2 PHARMACOKINETIC PROPERTIES
Cefixime, given orally, are about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. A single 200 mg tablet of cefixime produces an average peak serum concentration of approximately 2 mcg/mL (range 1 to 4 mcg/mL); a single 400 mg tablet produces an average peak concentration of approximately 3.7 mcg/mL (range 1.3 to 7.7 mcg/mL). The oral suspension produces average peak concentrations approximately 25% to 50% higher than the tablets, when tested in normal adult volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively, when tested in normal adult volunteers. The area under the time versus concentration curve (AUC) is greater by approximately 10% to 25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal adult volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media. Cross-over studies of tablet versus suspension have not been performed in children. Cefixime, given orally, are about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. A single 200 mg tablet of cefixime produces an average peak serum concentration of approximately 2 mcg/mL (range 1 to 4 mcg/mL); a single 400 mg tablet produces an average peak concentration of approximately 3.7 mcg/mL (range 1.3 to 7.7 mcg/mL). The oral suspension produces average peak concentrations approximately 25% to 50% higher than the tablets, when tested in normal adult volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively, when tested in normal adult volunteers. The area under the time versus concentration curve (AUC) is greater by approximately 10% to 25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal adult volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media. Cross-over studies of tablet versus suspension have not been performed in children.
Distribution
Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. Adequate data on CSF levels of cefixime are not available.
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 normal volunteers.
Special Populations
Geriatrics: Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults. Differences in the pharmacokinetic parameters between 12 young and 12 elderly subjects who received 400 mg of cefixime once daily for 5 days are summarized as follows:

Pharmacokinetic Parameters (mean ± SD) for Cefixime in Both Young & Elderly Subjects		
Pharmacokinetic parameter	**Young**	**Elderly**
C_{max} (mg/L)	4.74 ± 1.43	5.68 ± 1.83
T_{max} (h)*	3.9 ± 0.3	4.3 ± 0.6
AUC (mg.h/L)*	34.9 ± 12.2	49.5 ± 19.1
$T_{½}$ (h)*	3.5 ± 0.6	4.2 ± 0.4
C_{ave} (mg/L)*	1.42 ±0.50	1.99 ± 0.75
*Difference between age groups was significant. ($p<0.05$)		

6. NON CLINICAL PROPERTIES
Carcinogenesis, Mutagenesis, Impairment of Fertility
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
This product (Oral suspension) contains: Cefixime as active ingredient and it is indicated for the treatment of bacterial infections such as Acute exacerbations of chronic bronchitis; enteric (typhoid) fever; Community acquired pneumonia; ENT infections (e.g. otitis media, sinusitis, tonsillitis, pharyngitis, laryngitis); and urinary tract infections.
Bacteria possess a cell wall comprising a glycopeptide polymer commonly known as peptidoglycan, which is synthesized and remodelled through the action of a family of enzymes known as "penicillin-binding proteins" (PBPs). β-lactam antibiotics, including cephalosporins, are PBP inhibitors that, through inhibition of essential PBPs, result in impaired cell wall homeostasis, loss of cell integrity, and ultimately bacterial cell death
Molecular Formula – $C_{16}H_{15}N_5O_7S_2$
Molecular Weight – 453.5 g/mol
Chemical Structure



8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibility
None Stated.

8.2 Shelf Life
As per Carton.

8.3 Packaging Information
CEFXIATIM 100 DS is available in HDPE Bottle of 30ml packed in a carton along with Sterile Water for Reconstitution 30ml.

8.4 Storage Instructions
Store protected from moisture, at a temperature not exceeding 25°C.
After reconstitution keep suspension in refrigerator when not in use.
Use reconstituted suspension within 7 days. Any extra portion left to be thrown away.

Keep all medicines out of reach of children.

9. PATIENT COUNSELLING INFORMATION
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
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Marketed by:
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Telangana-500096.

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DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
26/1/AUSHADHI/87/2019/3291, 7/UA/LL/SC/P-2014, Date: 17/04/2026

DATE OF IMPLEMENTATION
May - 2026

Current Version: CEFXIATIM 100 DS_AKUMS_R1_P1

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