

# **CEFIXIME - cefixime powder, for suspension**

## **Aurobindo Pharma Limited**

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### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use CEFIXIME FOR ORAL SUSPENSION safely and effectively. See full prescribing information for CEFIXIME FOR ORAL SUSPENSION.**

**CEFIXIME for oral suspension**  
**Initial U.S. Approval: 1986**

### **INDICATIONS AND USAGE**

Cefixime for oral suspension is a cephalosporin antibacterial drug indicated in the treatment of adults and pediatric patients six months and older with the following infections:

- Uncomplicated Urinary Tract Infections (1.1)
- Otitis Media (1.2)
- Pharyngitis and Tonsillitis (1.3)
- Acute Exacerbations of Chronic Bronchitis (1.4)
- Uncomplicated Gonorrhea (cervical/urethral) (1.5)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefixime for oral suspension and other antibacterial drugs, cefixime for oral suspension should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. (1.6)

### **DOSAGE AND ADMINISTRATION**

- Adults: 400 mg daily (2.1)
- Pediatric patients (6 months and older): 8 mg/kg/day (2.2)

### **DOSAGE FORMS AND STRENGTHS**

- Oral Suspension: 100 mg/5 mL and 200 mg/5 mL (3)

### **CONTRAINDICATIONS**

- Contraindicated in patients with known allergy to cefixime or other cephalosporins. (4)

### **WARNINGS AND PRECAUTIONS**

- Hypersensitivity reactions including shock and fatalities have been reported with cefixime. Discontinue use if a reaction occurs. (5.1)
- *Clostridium difficile* associated diarrhea: Evaluate if diarrhea occurs. (5.2)

### **ADVERSE REACTIONS**

Most common adverse reactions are gastrointestinal such as diarrhea (16%), nausea (7%), loose stools (6%), abdominal pain (3%), dyspepsia (3%), and vomiting. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### **DRUG INTERACTIONS**

- Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. (7.1)
- Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly with warfarin and anticoagulants. (7.2)

### **USE IN SPECIFIC POPULATIONS**

- Pediatric Use: Efficacy and safety in infants younger than 6 months of age have not been established. (8.4)
- 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. (8.5)
- Renal Impairment: Cefixime may be administered in the presence of impaired renal function. Dose adjustment is required in patients whose creatinine clearance is less than 60 mL/min. (8.6)

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

- 1.1 Uncomplicated Urinary Tract Infections
- 1.2 Otitis Media
- 1.3 Pharyngitis and Tonsillitis
- 1.4 Acute Exacerbations of Chronic Bronchitis
- 1.5 Uncomplicated Gonorrhea (cervical/urethral)
- 1.6 Usage

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Adults
- 2.2 Pediatric Patients (6 months or older)
- 2.3 Renal Impairment
- 2.4 Reconstitution Directions for Oral Suspension

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Hypersensitivity Reactions
- 5.2 *Clostridium difficile*-Associated Diarrhea
- 5.3 Dose Adjustment in Renal Impairment
- 5.4 Coagulation Effects
- 5.5 Development of Drug-Resistant Bacteria

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience
- 6.2 Post-marketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Carbamazepine
- 7.2 Warfarin and Anticoagulants
- 7.3 Drug/Laboratory Test Interactions

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

## **15 REFERENCES**

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

## **17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

#### **1.1 Uncomplicated Urinary Tract Infections**

Cefixime for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated urinary tract infections caused by susceptible isolates of *Escherichia coli* and *Proteus mirabilis*.

#### **1.2 Otitis Media**

Cefixime for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with otitis media caused by susceptible isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*. (Efficacy for *Streptococcus pyogenes* in this organ system was studied in fewer than 10 infections.)

Note: For patients with otitis media caused by *Streptococcus pneumoniae*, overall response was approximately 10% lower for cefixime than for the comparator [see *Clinical Studies (14)*].

#### **1.3 Pharyngitis and Tonsillitis**

Cefixime for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with pharyngitis and tonsillitis caused by susceptible isolates of *Streptococcus pyogenes*. (Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections. Cefixime for oral suspension is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, data establishing the efficacy of cefixime for oral suspension in the subsequent prevention of rheumatic fever is not available.)

#### **1.4 Acute Exacerbations of Chronic Bronchitis**

Cefixime for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with acute exacerbations of chronic bronchitis caused by susceptible isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae*.

#### **1.5 Uncomplicated Gonorrhea (cervical/urethral)**

Cefixime for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated gonorrhea (cervical/urethral) caused by susceptible isolates of *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing isolates).

## 1.6 Usage

To reduce the development of drug resistant bacteria and maintain the effectiveness of cefixime for oral suspension and other antibacterial drugs, cefixime for oral suspension should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Adults

The recommended dose of cefixime is 400 mg daily. This may be given as a 400 mg tablet or capsule daily or the 400 mg tablet may be split and given as one half tablet every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended. The capsule and tablet may be administered without regard to food.

In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

### 2.2 Pediatric Patients (6 months or older)

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 hours.

Note: A suggested dose has been determined for each pediatric weight range. Refer to Table 1. Ensure all orders that specify a dose in milliliters include a concentration, because cefixime for oral suspension is available in three different concentrations (100 mg/5 mL, 200 mg/5 mL, and 500 mg/5 mL).

**Table 1. Suggested doses for pediatric patients**

<b>PEDIATRIC DOSAGE CHART</b>					
Doses are suggested for each weight range and rounded for ease of administration					
		<b>Cefixime for oral suspension</b>			<b>Cefixime chewable tablet</b>
		<b>100 mg/5 mL</b>	<b>200 mg/5 mL</b>	<b>500 mg/5 mL</b>	
<b>Patient Weight (kg)</b>	<b>Dose/Day (mg)</b>	<b>Dose/Day (mL)</b>	<b>Dose/Day (mL)</b>	<b>Dose/Day (mL)</b>	<b>Dose</b>
5 to 7.5*	50	2.5	--	--	--
7.6 to 10*	80	4	2	--	--

10.1 to 12.5	100	5	2.5	1	1 tablet of 100 mg
12.6 to 20.5	150	7.5	4	1.5	1 tablet of 150 mg
20.6 to 28	200	10	5	2	1 tablet of 200 mg
28.1 to 33	250	12.5	6	2.5	1 tablet of 100 mg and 1 tablet of 150 mg
33.1 to 40	300	15	7.5	3	2 tablets of 150 mg
40.1 to 45	350	17.5	9	3.5	1 tablet of 150 mg and 1 tablet of 200 mg
45.1 or greater	400	20	10	4	2 tablets of 200 mg

\* The preferred concentrations of oral suspension to use are 100 mg/5 mL or 200 mg/5 mL for pediatric patients in these weight ranges.

Children weighing more than 45 kg or older than 12 years should be treated with the recommended adult dose. Cefixime chewable tablets must be chewed or crushed before swallowing.

Otitis media should be treated with the chewable tablets or suspension. Clinical trials of otitis media were conducted with the chewable tablets or suspension, and the chewable tablets or suspension results in higher peak blood levels than the tablet when administered at the same dose.

Therefore, the tablet or capsule should not be substituted for the chewable tablets or suspension in the treatment of otitis media [see *Clinical Pharmacology (12.3)*].

In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

### 2.3 Renal Impairment

Cefixime for oral suspension may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Refer to Table 2 for dose adjustments for adults with renal impairment. Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.

**Table 2. Doses for Adults with Renal Impairment**

<b>Renal Dysfunction</b>	<b>Cefixime for oral suspension</b>			<b>Tablet</b>	<b>Chewable Tablet</b>
	<b>100 mg/5 mL</b>	<b>200 mg/5 mL</b>	<b>500 mg/5 mL</b>	<b>400 mg</b>	<b>200 mg</b>
Creatinine Clearance (mL/min)					

	Dose/Day (mL)	Dose/Day (mL)	Dose/Day (mL)	Dose/Day	Dose/Day
60 or greater	Normal dose	Normal dose	Normal dose	Normal dose	Normal dose
21 to 59* OR renal hemodialysis*	13	6.5	2.6	Not Appropriate	Not Appropriate
20 or less OR continuous peritoneal dialysis	8.6	4.4	1.8	0.5 tablet	1 tablet

\* The preferred concentrations of oral suspension to use are 200 mg/5 mL or 500 mg/5 mL for patients with this renal dysfunction

## 2.4 Reconstitution Directions for Oral Suspension

Strength	Bottle Size	Reconstitution Directions
100 mg/5 mL	100 mL	To reconstitute, suspend with <b>70 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
200 mg/5 mL	75 mL	To reconstitute, suspend with <b>52.5 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
100 mg/5 mL and 200 mg/5 mL	50 mL	To reconstitute, suspend with <b>35 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.

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.

## 3 DOSAGE FORMS AND STRENGTHS

Cefixime is available for oral administration in the following strengths:

- Powder for oral suspension, when reconstituted, provides either 100 mg/5 mL or

200 mg/5 mL of cefixime as trihydrate. The powder has an off-white to pale yellow color and is strawberry flavored.

## **4 CONTRAINDICATIONS**

Cefixime for oral suspension is contraindicated in patients with known allergy to cefixime or other cephalosporins.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 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.

### **5.2 *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.

### **5.3 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 [see *Dosage and Administration (2)*].

### **5.4 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.

## **5.5 Development of Drug-Resistant Bacteria**

Prescribing 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.

## **6 ADVERSE REACTIONS**

### **6.1 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.

### **6.2 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 [*see Dosage and Administration (2) and Overdosage (10)*]. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

## **7 DRUG INTERACTIONS**

### **7.1 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.

### **7.2 Warfarin and Anticoagulants**

Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

## 7.3 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.

The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest<sup>®\*\*</sup>, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix<sup>®\*\*</sup> or TesTape<sup>®\*\*</sup>) be used. A false-positive direct Coombs test has been reported during treatment with other cephalosporins; therefore, it should be recognized that a positive Coombs test may be due to the drug.

\*\* Clinitest<sup>®</sup> and Clinistix<sup>®</sup> are registered trademarks of Ames Division, Miles Laboratories, Inc. Tes-Tape<sup>®</sup> is a registered trademark of Eli Lilly and Company.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available data from published observational studies, case series, and case reports over several decades with cephalosporin use, including cefixime, in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*). Reproduction studies have been performed in mice and rats at doses equivalent to 40 and 80 times, respectively, the adult human recommended dose and have revealed no evidence of harm to the fetus due to cefixime (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Clinical Considerations

##### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

Maternal gonorrhea may be associated with preterm birth, low neonatal birth weight, chorioamnionitis, intrauterine growth restriction, small for gestational age and premature rupture of membranes. Perinatal transmission of gonorrhea to the offspring can result in infant blindness, joint infections, and bloodstream infections.

## Data

### *Human Data*

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified a consistent association with cephalosporin use, including cefixime, during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodological limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

### *Animal data*

The results of embryo-fetal development studies in mice and rats show that cefixime, at doses up to 3200 mg/kg/day administered during the period of organogenesis did not adversely affect development. In these studies, in mice and rats, cefixime did not affect postnatal development or reproductive capacity of the F<sub>1</sub> generation or fetal development of the F<sub>2</sub> generation. In an embryo-fetal development study in rabbits, cefixime at doses of 3.2, 10 or 32 mg/kg given daily during the period of organogenesis (gestation days 6 through 18) resulted in abortions and/or maternal deaths at doses > 10 mg/kg (typically associated with the administration of antibiotics in this species), but no malformations were reported at lower doses. A pre- and post-natal development study of cefixime at oral doses up to 3200 mg/kg/day in rats demonstrated no effect on the duration of pregnancy, process of parturition, development and viability of offspring, or reproductive capacity of the F<sub>1</sub> generation and development of their fetuses (F<sub>2</sub>).

## **8.2 Lactation**

### Risk Summary

There are no available data on the presence of cefixime in human milk, the effects on the breastfed infant, or the effects on milk production. Cefixime is present in animal milk (*see Data*). When a drug is present in animal milk, it is likely the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cefixime and any potential adverse effects on the breastfed infant from cefixime or from the mother's underlying condition.

### Data

In a study on disposition of cefixime in pregnant and lactating rats, continuous intra-peritoneal infusion of 2.54 mg/kg/day of <sup>14</sup>C-cefixime from days 10 to 14 postpartum resulted in steady state plasma concentrations of radioactivity in the dams that were 70 times greater than in their nursing pups.

After 102 hours of drug infusion, total radioactivity in the body of the pups, including the stomach and intestinal contents, was 1.5% of the <sup>14</sup>C-cefixime estimated to be in the

mother's body at steady state.<sup>1</sup>

#### **8.4 Pediatric Use**

Safety and effectiveness of cefixime in pediatric patients younger than 6 months of age 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.

#### **8.5 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 [see *Clinical Pharmacology (12.3)*]. These differences were small and do not indicate a need for dosage adjustment of the drug in the elderly.

#### **8.6 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 [see *Dosage and Administration (2.3)*].

### **10 OVERDOSAGE**

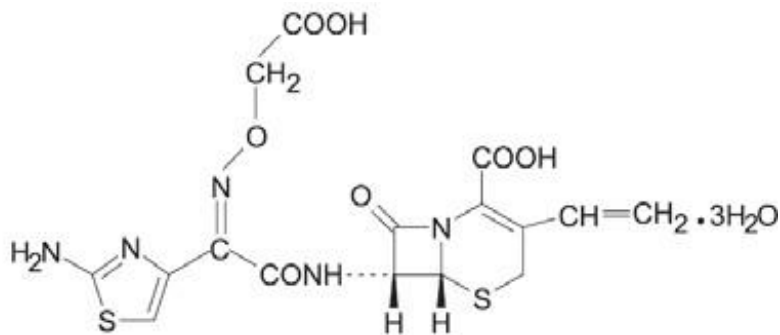
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ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

### **11 DESCRIPTION**

Cefixime is a semisynthetic, cephalosporin antibacterial for oral administration. Chemically, it is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7<sup>2</sup>-(*Z*)-[*O*-(carboxy methyl) oxime] trihydrate.

Molecular weight = 507.50 as the trihydrate. Chemical Formula is C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>7</sub>S<sub>2</sub>·3H<sub>2</sub>O.

The structural formula for cefixime is:



- Inactive ingredients contained in cefixime powder for oral suspension USP are: colloidal silicon dioxide, strawberry guarana flavor, sucrose, and xanthan gum.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Cefixime is a semisynthetic cephalosporin antibacterial drug [see *Microbiology (12.4)*].

### 12.3 Pharmacokinetics

Cefixime chewable tablets are bioequivalent to oral suspension.

Cefixime tablets and suspension, 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 [see *Dosage and Administration (2)*]. Cross-over studies of tablet versus suspension have not been performed in children.

The 400 mg capsule is bioequivalent to the 400 mg tablet under fasting conditions. However, food reduces the absorption following administration of the capsule by approximately 15% based on AUC and 25% based on  $C_{max}$ .

Peak serum concentrations occur between 2 and 6 hours following oral administration

of a single 200 mg tablet, a single 400 mg tablet or 400 mg of cefixime suspension. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension. Peak serum concentrations occur between 3 and 8 hours following oral administration of a single 400 mg capsule.

### **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:

<b>Pharmacokinetic Parameters (mean <math>\pm</math> SD) for Cefixime in Both Young &amp; Elderly Subjects</b>		
<b>Pharmacokinetic parameter</b>	<b>Young</b>	<b>Elderly</b>
$C_{max}$ (mg/L)	4.74 $\pm$ 1.43	5.68 $\pm$ 1.83
$T_{max}$ (h)*	3.9 $\pm$ 0.3	4.3 $\pm$ 0.6
AUC (mg.h/L)*	34.9 $\pm$ 12.2	49.5 $\pm$ 19.1
$T_{1/2}$ (h)*	3.5 $\pm$ 0.6	4.2 $\pm$ 0.4
$C_{ave}$ (mg/L)*	1.42 $\pm$ 0.5	1.99 $\pm$ 0.75

\* Difference between age groups was significant. ( $p < 0.05$ )

However, these increases were not clinically significant [see *Dosage and Administration* (2)].

**Renal Impairment:** In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the

blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21 to 60 mL/min.

## 12.4 Microbiology

### Mechanism of Action

As with other cephalosporins, the bactericidal action of cefixime results from inhibition of cell wall synthesis. Cefixime is stable in the presence of certain beta-lactamase enzymes. As a result, certain organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases may be susceptible to cefixime.

### Resistance

Resistance to cefixime in isolates of *Haemophilus influenzae* and *Neisseria gonorrhoeae* is most often associated with alterations in penicillin-binding proteins (PBPs). Cefixime may have limited activity against Enterobacteriaceae producing extended spectrum beta-lactamases (ESBLs). *Pseudomonas* species, *Enterococcus* species, strains of Group D streptococci, *Listeria monocytogenes*, most strains of staphylococci (including methicillin-resistant strains), most strains of *Enterobacter* species, most strains of *Bacteroides fragilis*, and most strains of *Clostridium* species are resistant to cefixime.

### Antimicrobial Activity

Cefixime has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

#### Gram-positive Bacteria

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

#### Gram-negative Bacteria

*Escherichia coli*

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Neisseria gonorrhoeae*

*Proteus mirabilis*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefixime against isolates of similar genus or organism group. However, the efficacy of cefixime in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria

*Streptococcus agalactiae*

Gram-negative Bacteria

*Citrobacter amalonaticus*

*Citrobacter diversus*

*Haemophilus parainfluenzae*

*Klebsiella oxytoca*

*Klebsiella pneumoniae*

*Pasteurella multocida*

*Proteus vulgaris*

*Providencia* species

*Salmonella* species

*Serratia marcescens*

*Shigella* species

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 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 the fertility and reproductive performance study in rats, no difference between control and drug-treated animals was detected in mating behavior, pregnancy rate, or litter parameters (determined at sacrifice on day 13 of pregnancy) at oral doses up to 1000 mg/kg/day (25 times the adult therapeutic dose) administered to males (for 68 days prior to pairing and during the cohabitation period) and females (for 14 days before pairing to weaning).

## **14 CLINICAL STUDIES**

Comparative clinical trials of otitis media were conducted in nearly 400 children between the ages of 6 months to 10 years. *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella catarrhalis* from 15% and *S.*



*pyogenes* from 4%.

The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae* or *Moraxella catarrhalis* approximately 7% higher (12% when beta-lactamase positive isolates of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg twice a day or 8 mg/kg once a day, or with a comparator. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibacterial drug) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

#### **Bacteriological Outcome of Otitis Media at Two to Four Weeks Post-Therapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome**

<b>Organism</b>	<b>Cefixime(a) 4 mg/kg BID</b>	<b>Cefixime(a) 8 mg/kg QD</b>	<b>Control(a) drugs</b>
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 (b)
<i>Moraxella catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>S. pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive isolates of *Haemophilus influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibacterial drug. In nineteen of these, the clinical course could be assessed and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

## **15 REFERENCES**

1. Halperin-Walega, E. Batra VK, Tonelli AP, Barr A, Yacobi A. 'Disposition of Cefixime in the Pregnant and Lactating Rat. Transfer to the Fetus and Nursing Pup'. *Drug Metabolism and Disposition*. 1988;16(1):pp130-134.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

**Cefixime for oral suspension USP 100 mg/5 mL** is off-white to pale yellow colored powder - Each 5 mL of reconstituted off-white to pale yellow, strawberry flavored suspension contains cefixime trihydrate equivalent to 100 mg cefixime.

50 mL Bottles	NDC 65862-751-50
100 mL Bottles	NDC 65862-751-01

**Cefixime for oral suspension USP 200 mg/5 mL** is off-white to pale yellow colored powder - Each 5 mL of reconstituted off-white to pale yellow, strawberry flavored suspension contains cefixime trihydrate equivalent to 200 mg cefixime.

50 mL Bottles	NDC 65862-752-50
75 mL Bottles	NDC 65862-752-75

## **Storage**

Prior to Reconstitution: Store drug powder at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

After Reconstitution: Store at room temperature or under refrigeration. Shake well before using. Discard unused portion after 14 days.

Keep tightly closed.

## **17 PATIENT COUNSELING INFORMATION**

### Drug Resistance

Patients should be counseled that antibacterial drugs, including cefixime, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefixime 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: (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefixime for oral suspension or other antibacterial drugs in the future.

### Diarrhea

Advise patients 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 should contact their physician as soon as possible.

Distributed by:

**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520

Manufactured by:  
**Aurobindo Pharma Limited**  
Hyderabad-500 032, India

Revised: 10/2021

**PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 100 mg/5 mL (50 mL Bottle)**

**NDC 65862-751-50**

**Rx only**

**Cefixime for  
Oral Suspension, USP  
100 mg/5 mL**

**when reconstituted**

FOR ORAL USE ONLY

SHAKE WELL BEFORE USING

**AUROBINDO 50 mL**

**(when reconstituted)**

NDC 65862-751-50

**Rx only**  
**Cefixime for  
Oral Suspension, USP**  
**100 mg/5 mL**  
when reconstituted  
FOR ORAL USE ONLY  
SHAKE WELL BEFORE USING  
**AUROBINDO 50 mL**  
(when reconstituted)

Each 5 mL (teaspoonful) of reconstituted suspension contains cefixime trihydrate equivalent to 100 mg cefixime.  
**Net Contents:** Contains 1 g cefixime as trihydrate  
**Usual Dosage:** See package insert.  
**Directions for mixing:** To reconstitute, suspend with **35 mL water.**  
**Method:** Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.  
**Prior to reconstitution:** Store drug powder at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature].  
**After reconstitution:** Store at room temperature or under refrigeration.  
Keep tightly closed.  
Discard any unused portion after 14 days.  
**TO THE PHARMACIST:**  
**IMPORTANT**  
Use this bottle for dispensing. Use only if inner seal is intact.

Distributed by:  
**Aurobindo Pharma USA, Inc.**  
279 Princeton-Hightstown Road  
East Windsor, NJ 08520

Made in India

Code: TS/DRUGS/78/1996

Date of reconstitution: \_\_\_\_\_

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\* Over Printing Zone

**Coding Area**  
(45 x 20 mm)  
Dotted line not to be printed

**PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 200 mg/5 mL (50 mL Bottle)**

**NDC 65862-752-50**

**Rx only**

**Cefixime for  
Oral Suspension, USP  
200 mg/5 mL**

**when reconstituted**  
**FOR ORAL USE ONLY**  
**SHAKE WELL BEFORE USING**  
**AUROBINDO 50 mL**  
**(when reconstituted)**

NDC 65862-752-50

**Rx only**  
**Cefixime for Oral Suspension, USP**  
**200 mg/5 mL**

**when reconstituted**  
**FOR ORAL USE ONLY**  
**SHAKE WELL BEFORE USING**  
**50 mL**  
**(when reconstituted)**

**Each 5 mL** (teaspoonful) of reconstituted suspension contains cefixime trihydrate equivalent to 200 mg cefixime.  
**Net Contents:** Contains 2 g cefixime as trihydrate  
**Usual Dosage:** See package insert.  
**Directions for mixing:** To reconstitute, suspend with **35 mL water**.  
**Method:** Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.  
**Prior to reconstitution:** Store drug powder at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature].  
**After reconstitution:** Store at room temperature or under refrigeration.  
 Keep tightly closed.  
 Discard any unused portion after 14 days.

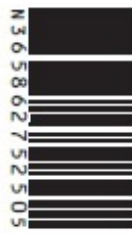
Distributed by:  
**Aurobindo Pharma USA, Inc.**  
 279 Princeton-Hightstown Road  
 East Windsor, NJ 08520

Made in India  
 Code: TS/DRUGS/78/1996  
 Date of reconstitution: \_\_\_\_\_

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\* Over Printing Zone

Coding Area  
 (45 x 20 mm)  
 Dotted line not to be printed



## CEFIXIME

cefixime powder, for suspension

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:65862-751
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>CEFIXIME</b> (UNII: 9711C92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	100 mg in 5 mL

### Inactive Ingredients

Ingredient Name	Strength
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>STRAWBERRY</b> (UNII: 4J2TY8Y81V)	
<b>SUCROSE</b> (UNII: C151H8M554)	
<b>XANTHAN GUM</b> (UNII: TTV12P4NEE)	

### Product Characteristics

<b>Color</b>	WHITE (Off-white to pale yellow)	<b>Score</b>	
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<b>Shape</b>		<b>Size</b>		
<b>Flavor</b>	STRAWBERRY	<b>Imprint Code</b>		
<b>Contains</b>				
<b>Packaging</b>				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-751-50	50 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2015	
2	NDC:65862-751-01	100 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2015	
<b>Marketing Information</b>				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA204835	04/14/2015		

## CEFIXIME

cefixime powder, for suspension

<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:65862-752
<b>Route of Administration</b>	ORAL		
<b>Active Ingredient/Active Moiety</b>			
Ingredient Name	Basis of Strength	Strength	
<b>CEFIXIME</b> (UNII: 9711C92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	200 mg in 5 mL	
<b>Inactive Ingredients</b>			
Ingredient Name	Strength		
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)			
<b>STRAWBERRY</b> (UNII: 4J2TY8Y81V)			
<b>SUCROSE</b> (UNII: C151H8M554)			
<b>XANTHAN GUM</b> (UNII: TTV12P4NEE)			
<b>Product Characteristics</b>			
<b>Color</b>	WHITE (Off-white to pale yellow)	<b>Score</b>	
<b>Shape</b>		<b>Size</b>	
<b>Flavor</b>	STRAWBERRY	<b>Imprint Code</b>	
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-752-50	50 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2015	
2	NDC:65862-752-75	75 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2015	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204835	04/14/2015	

**Labeler** - Aurobindo Pharma Limited (650082092)

## Establishment

Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917639	ANALYSIS(65862-751, 65862-752) , MANUFACTURE(65862-751, 65862-752)

Revised: 2/2024

Aurobindo Pharma Limited