CEFIXIME- cefixime powder, for suspension
Belcher Pharmaceuticals,LLC

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.

CEFIXIMEfor Oral Suspension USP, 100 mg/5 mL

CEFIXIMEfor Oral Suspension USP, 200 mg/5 mL

For oral administration

Initial U.S. Approval:1986

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

INDICATIONS AND USAGE

Cefixime for oral suspension, USP is a cephalosporin antibacterial drug indicated for
• 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)

DOSAGE AND ADMINISTRATION

• Adults: 400 mg daily (2.1)
• Children: 8 mg/kg/day (2.2) (2)

DOSAGE FORMS AND STRENGTHS

- Oral Suspension: 100 mg/5 mL, 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 Belcher Pharmaceuticals, LLC at 1-727-471-0850 or FDA at 1-800-FDA-1088 or *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

- Pregnancy: Cefixime should be used during pregnancy only if clearly needed. (8.1)
- Nursing Mothers: Consideration should be given to discontinuing nursing temporarily during treatment with cefixime. (8.3)
- Children: Efficacy and safety in infants aged less than six months 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND 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.

Cefixime for oral suspension is a cephalosporin antibacterial drug indicated in the treatment of adults and pediatric patients six months of age or older with the following infections when caused by susceptible isolates of the designated bacteria:

1.1 Uncomplicated Urinary Tract Infections

Uncomplicated Urinary Tract Infections caused by *Escherichia coli*and *Proteus mirabilis*

1.2 Otitis Media

Otitis media caused by *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

Pharyngitis and Tonsillitis caused by *Streptococcus pyogenes*. (Note: Penicillin is the usual drug of choice in the treatment of *Streptococcuspyogenes*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

Acute Exacerbations of Chronic Bronchitis caused by *Streptococcus pneumoniae*and *Haemophilus influenzae*.

1.5 Uncomplicated Gonorrhea (cervical/urethral)

Uncomplicated Gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoeae*(penicillinase –and non- penicillinase-producing isolates).

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 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 two different concentrations (100 mg/5 mL, 200 mg/5 mL).

Table 1. Suggested doses for pediatric patients

PEDIATRIC DOSAGE CHART Doses are suggested for each weight range and rounded for ease of administration

		Cefixime for Oral Suspension		Cefixime Chewable Tablet
Patient Weight (kg)	Dose/Day (mg)	100 mg/5 mL Dose/Day (mL)	200 mg/5 mL Dose/Day (mL)	Dose
5 to 7.5*	50	2.5	--	--
7.6 to 10*	80	4	2	--
10.1 to 12.5	100	5	2.5	1 tablet of 100 mg
12.6 to 20.5	150	7.5	4	1 tablet of 150 mg
20.6 to 28	200	10	5	1 tablet of 200 mg
28.1 to 33	250	12.5	6	1 tablet of 100 mg and 1 tablet of 150 mg
33.1 to 40	300	15	7.5	2 tablets of 150 mg
40.1 to 45	350	17.5	9	1 tablet of 150 mg and 1 tablet of 200 mg
45.1 or greater	400	20	10	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

Renal Dysfunction	Cefixime for Oral Suspension		Tablet	Chewable Tablet
Creatinine Clearance (mL/min)	100 mg/5 mL Dose/Day (mL)	200 mg/5 mL Dose/Day (mL)	400 mg Dose/Day	200 mg Dose/Day
60 or greater	Normal dose	Normal dose	Normal dose	Normal dose
21 to 59* OR renal hemodialysis*	13	6.5	Not Appropriate	Not Appropriate
20 or less OR continuous peritoneal dialysis	8.6	4.4	0.5 tablet	1 tablet

* The preferred concentration of oral suspension to use is 200 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 and 200 mg/5 mL	100 mL	To reconstitute, suspend with **68 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.
100 mg/5 mL and 200 mg/5 mL	75 mL	To reconstitute, suspend with **51 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.
100 mg/5 mL and 200 mg/5 mL	50 mL	To reconstitute, suspend with **34 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.

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 for oral suspension,USP is available for oral administration in the following dosage forms and strengths:

- Powder for oral suspension, when reconstituted, provides either 100 mg/5 mL or 200 mg/5 mL of cefixime as trihydrate. For 100 mg/5 mL and 200 mg/5 mL, 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 for oral suspension 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 antibiotics 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 for oral suspension 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 for oral suspension 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 antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C.difficile*may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C.difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Dose Adjustment in Renal Impairment

The dose of Cefixime for oral suspension 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 for oral suspension 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 for oral suspension 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 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®**, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or TesTape®**) 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® and Clinistix® are registered trademarks of Ames Division, Miles Laboratories, Inc. Tes-Tape® is a registered trademark of Eli Lilly and Company.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.2 Labor And Delivery

Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

8.3 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.

8.4 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.

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)*].

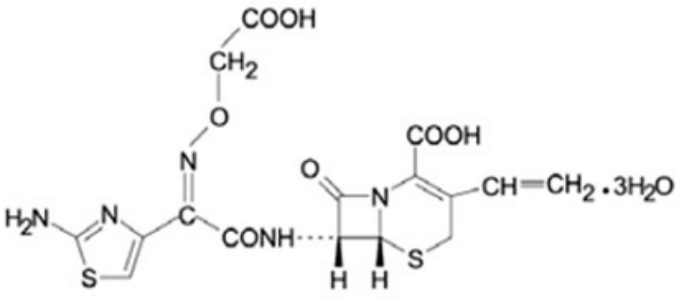
10 OVERDOSAGE

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 (*6R,7R*)-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 ^{2}-(*Z*)-[O-(carboxy methyl) oxime] trihydrate.

Molecular weight = 507.50 as the trihydrate. Chemical Formula is $C_{16}H_{15}N_5O_7S_2.3H_2O$
The structural formula for cefixime is:



Inactive ingredients contained in cefixime powder for oral suspension, USP are: colloidal silicon dioxide, sodium benzoate, strawberry 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:

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
$T_{1/2}$(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. ($p<0.05$)

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 due to 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 Test Methods

When available, the clinical microbiology laboratory should provide cumulative reports of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method [1,2] (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. [2,3] This procedure uses paper disks impregnated with 5 mcg cefixime to test the susceptibility of bacteria to cefixime. The disc diffusion breakpoints are provided in Table 3.

Table 3: Susceptibility Interpretive Criteria for Cefixime

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R

Enterobacteriaceae[1]	≤1	2	≥4	≥19	16 to 18	≤15
Haemophilus influenzae[2,3]	≤1	NA	NA	≥21	NA	NA
Neisseria gonorrhoeae[3,4]	≤0.25	NA	NA	≥31	NA	NA

[1]Do not test *Morganella*species by disk diffusion
[2]Test *Haemophilus influenzae*using Haemophilus Test Medium (HTM)
[3]The current absence of resistant isolates precludes defining any results other than "susceptible" Isolates
yielding results other than susceptible should be subjected to additional testing.
[4]Test *Neisseria gonorrhoeae*using GC agar base and 1% defined growth supplement. Minimum
inhibitory concentrations are determined using the agar dilution method.

A report of *Susceptible (S*) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate (I)*indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant (R)*indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. [1,2,3]Standard cefixime powder should provide the following range of MIC values noted in Table 4. For the diffusion technique using the 5 mcg disk, the criteria in Table 4 should be achieved.

Table 4: Acceptable Quality Control Ranges for Cefixime

Quality Control Organisms	**Minimum Inhibitory Concentrations (mcg/mL)**	**Disk Diffusion Zone Diameter (mm)**
*E. coli*ATCC 25922	0.25 to 1	23 to 27
*H. influenzae*ATCC 49247	0.12 to 1	25 to 33
*N. gonorrhoeae*ATCC 49226	0.004 to 0.03	37 to 45
*S. pneumoniae*ATCC 49619	NA	16 to 23
*S. aureus*ATCC 29213	8 to 32	NA

ATCC = American Type Culture Collection

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 rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

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 antibiotic) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30%-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

Organism	Cefixime(a) 4 mg/kg BID	Cefixime(a) 8 mg/kg QD	Control(a) drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
*Haemophilus influenzae*beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
*Haemophilus influenzae*beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 (b)
Moraxella catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S.pyogenes	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 antibiotic. 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. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement, CLSI document M100-S25, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard - Twelfth Edition. CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefixime for oral suspension, USP is available for oral administration in following dosage forms, strengths and packages listed in the table below:

Dosage Form	Strength	Description	Package Size	NDC Code	Storage
Cefixime for Oral Suspension,USP	100mg/5mL	Off-white to pale yellow colored powder. After reconstituted as directed, each 5 mL of reconstituted suspension contains 100 mg of cefixime as the trihydrate.	Bottle of 50 mL	62250-663-26	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.
			Bottle of 75 mL	62250-663-27	
			Bottle of 100 mL	62250-663-28	
	200 mg/5mL	Off-white to pale yellow colored powder. After reconstituted as directed, each 5 mL of reconstituted suspension contains 200 mg of cefixime as the trihydrate.	Bottle of 50 mL	62250-664-26	
			Bottle of 75 mL	62250-664-27	
			Bottle of 100 mL	62250-664-28	

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

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 cefixime chewable tablets or other antibacterial drugs in the future.

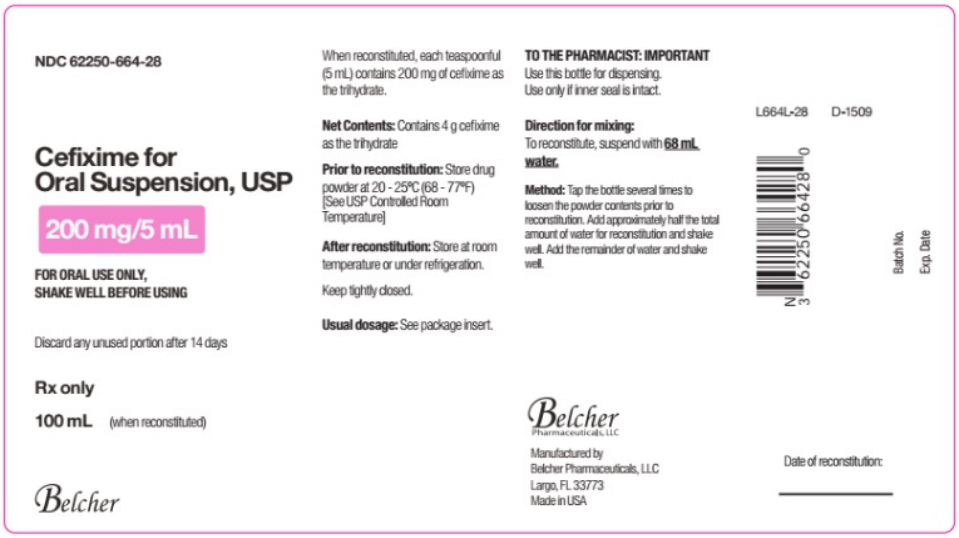
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Products	Manufactured by:
Cefixime for Oral Suspension USP, 200 mg/5mL	Belcher Pharmaceuticals,LLC 12393 Belcher Road Suite # 420 Largo FL-33773
Cefixime for Oral Suspension USP, 100 mg/5mL	

CEFIXIME FOR ORAL SUSPENSION, USP
200 mg/5 mL
Rx only
NDC 62250-664-26: Bottle of **50 mL**

CEFIXIME FOR ORAL SUSPENSION, USP
200 mg/5 mL
Rx only
NDC 62250-664-27: Bottle of **75 mL**

CEFIXIME FOR ORAL SUSPENSION, USP
200 mg/5 mL
Rx only
NDC 622650-664-28: Bottle of **100 mL**



CEFIXIME

cefixime powder, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:62250-663
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CEFIXIME (UNII: 97I1C92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	100 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM BENZOATE (UNII: OJ245FE5EU)	
STRAWBERRY (UNII: 4J2TY8Y81V)	
SUCROSE (UNII: C151H8M554)	
XANTHAN GUM (UNII: TTV12P4NEE)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	white (Off White to Pale Yellow Powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:62250-663-28	100 mL in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	03/15/2017	
2	NDC:62250-663-27	75 mL in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	03/15/2017	
3	NDC:62250-663-26	50 mL in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	03/15/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206938	03/15/2017	

CEFIXIME

cefixime powder, for suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:62250-664
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CEFIXIME (UNII: 97I1C92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	200 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM BENZOATE (UNII: OJ245FE5EU)	
STRAWBERRY (UNII: 4J2TY8Y81V)	
SUCROSE (UNII: C151H8M554)	
XANTHAN GUM (UNII: TTV12P4NEE)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	white (Off White to Pale Yellow Powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:62250-664-28	100 mL in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	03/15/2017	
2	NDC:62250-664-27	75 mL in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	03/15/2017	
3	NDC:62250-664-26	50 mL in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	03/15/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206938	03/15/2017	

Labeler - Belcher Pharmaceuticals,LLC (965082543)

Establishment

Name	Address	ID/FEI	Business Operations
Belcher Pharmaceuticals,LLC		965082543	analysis(62250-663, 62250-664) , manufacture(62250-663, 62250-664)