

CEFIXIME- cefixime powder, for suspension
CEFIXIME- cefixime capsule
Lupin Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CEFIXIME for oral suspension, 100 mg/5 mL
CEFIXIME for oral suspension, 200 mg/5 mL
CEFIXIME capsules, 400 mg
For oral administration

Initial U.S. Approval: 1986

INDICATIONS AND USAGE

Cefixime 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 and other antibacterial drugs, cefixime for oral suspension and cefixime capsules 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)
- Capsules: 400mg (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 Lupin Pharmaceuticals, Inc. at 1-800-399-2561 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: 11/2018

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 Labor and Delivery
- 8.3 Nursing Mothers
- 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

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Uncomplicated Urinary Tract Infections

Cefixime for oral suspension and cefixime capsule 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 and cefixime capsule 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 and cefixime capsule 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 and cefixime capsule is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, data establishing the efficacy of cefixime for oral suspension and cefixime capsule in the subsequent prevention of rheumatic fever is not available.)

1.4 Acute Exacerbations of Chronic Bronchitis

Cefixime for oral suspension and cefixime capsule 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 and cefixime capsule 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 and other antibacterial drugs, cefixime for oral suspension and cefixime capsule 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 capsule daily. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.

The capsule 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 and 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	
		100 mg/5 mL	200 mg/5 mL
Patient Weight (kg)	Dose/Day (mg)	Dose/Day (mL)	Dose/Day (mL)
5 to 7.5	50	2.5	--
7.6 to 10	80	4	2
10.1 to 12.5	100	5	2.5
12.6 to 20.5	150	7.5	4
20.6 to 28	200	10	5
28.1 to 33	250	12.5	6
33.1 to 40	300	15	7.5
40.1 to 45	350	17.5	9
45.1 or greater	400	20	10

Children weighing more than 45 kg or older than 12 years should be treated with the recommended adult

dose.

Otitis media should be treated with the suspension. Clinical trials of otitis media were conducted with the suspension, and the 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 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 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	
	100 mg/5 mL	200 mg/5 mL
Creatinine Clearance (mL/min)	Dose/Day (mL)	Dose/Day (mL)
60 or greater	Normal dose	Normal dose
21 to 59* OR renal hemodialysis*	13	6.5
20 or less	8.6	4.4
OR continuous peritoneal dialysis		

* 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
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 a 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.

Cefixime capsule is available for oral administration as capsules which provide 400 mg of cefixime as trihydrate. These are size "00EL" capsules with pink opaque cap and pink opaque body with "LU" on the cap and "U43" on the body in black ink. Capsules contain white to yellowish white granular powder.

4 CONTRAINDICATIONS

Cefixime 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[®], 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. TesTape[®] 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

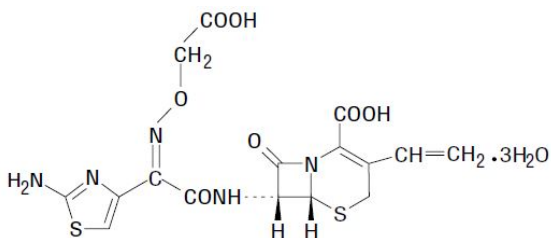
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ 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 (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, 7²-(*Z*)-[O-(carboxy methyl) oxime] trihydrate.

Molecular weight = 507.50 as the trihydrate. Chemical Formula is C₁₆H₁₅N₅O₇S₂·3H₂O

The structural formula for cefixime is:



Inactive ingredients contained in the cefixime powder for oral suspension USP are colloidal silicon dioxide, sodium benzoate, strawberry flavor, sucrose, and xanthan gum.

Inactive ingredients contained in the cefixime capsules 400 mg are colloidal silicon dioxide, crospovidone, low substituted hydroxy propyl cellulose, magnesium stearate, and mannitol. The capsule shell contains the following inactive ingredients: ferric oxide black, ferric oxide red, gelatin, potassium hydroxide, propylene glycol, shellac, sodium lauryl sulfate, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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 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 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 antibacterial drug) 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
<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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefixime for oral suspension USP, 100 mg/5 mL is an 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 and is supplied as follows:

NDC 68180-405-01 - 50 mL Bottle

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.

Cefixime for oral suspension USP, 200 mg/5 mL is an 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 and is supplied as follows:

NDC 68180-407-03 - 50 mL Bottle

NDC 68180-407-04 - 75 mL Bottle

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.

Cefixime capsules, 400 mg is an size "00EL" capsules with pink opaque cap and pink opaque body, imprinted with "LU" on cap and "U43" on body in black ink, containing white to yellowish white granular powder containing 400 mg of cefixime as the trihydrate and is supplied as follows:

NDC 68180-416-08 - Bottle of 50 capsules

NDC 68180-416-11 - Unit dose Package of 10 (1 blister of 10 capsules)

Store at 20 to 25°C (68 to 77°F) [See USP Controlled Temperature].

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Counsel patients 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.

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.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Mandideep 462 046

INDIA

Revised: October 2018

ID#: 257765

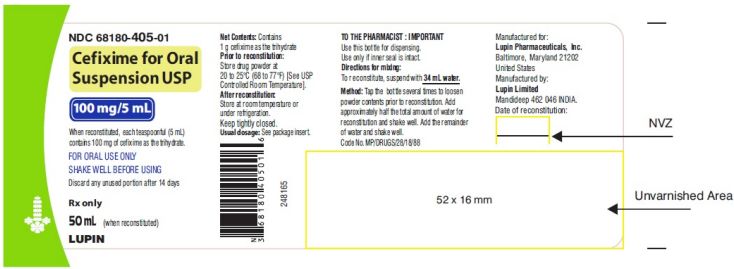
PACKAGE LABEL/PRINCIPAL DISPLAY PANEL

CEFIXIME FOR ORAL SUSPENSION USP

100 mg/5 mL

Rx only

NDC 68180-405-01: Bottle of 50 mL



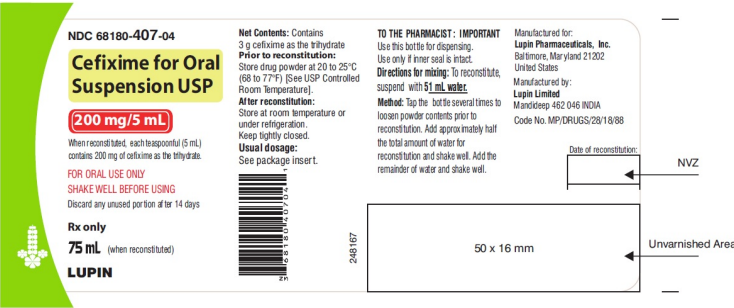
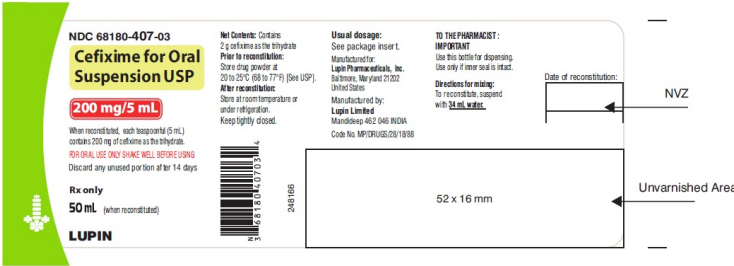
CEFIXIME FOR ORAL SUSPENSION USP

200 mg/5 mL

Rx only

NDC 68180-407-03: Bottle of 50 mL

NDC 68180-407-04: Bottle of 75 mL



CEFIXIME CAPSULES

400 mg

Rx only

NDC 68180-416-08 - Bottle of 50 capsules



CEFIXIME CAPSULES

400 mg

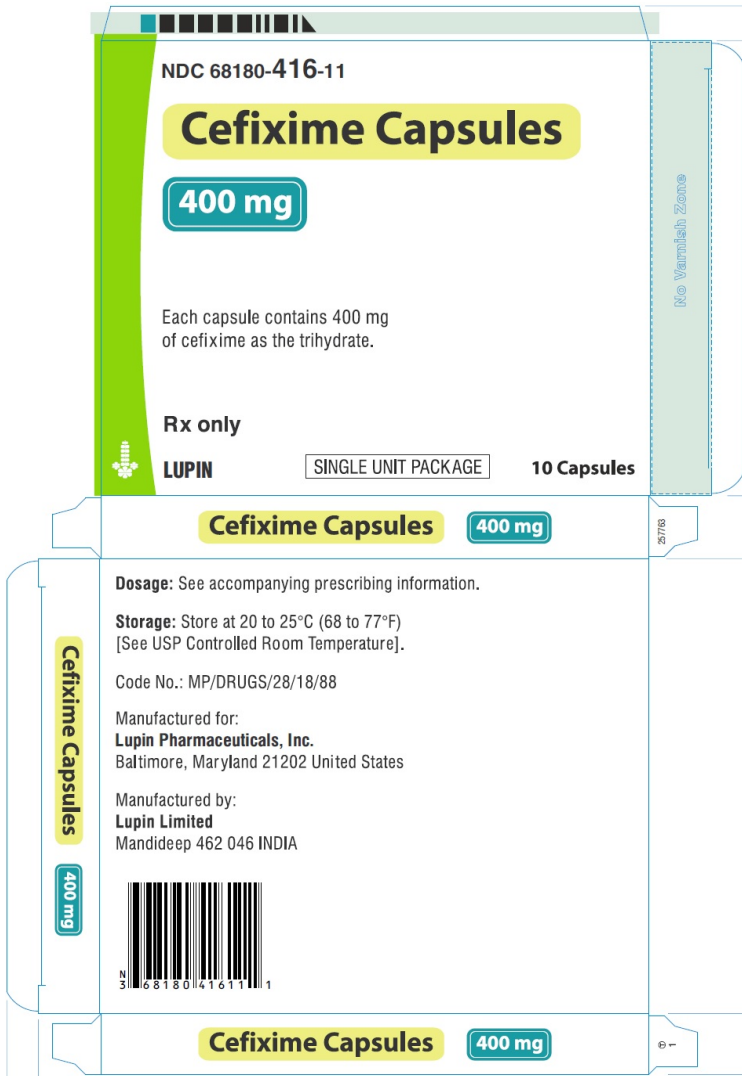
Rx only

NDC 68180-416-11 - Blister

Unit dose Package of 10 (1 blister of 10 capsules)



CEFIXIME CAPSULES
 400 mg
 Rx only
 NDC 68180-416-11 - Carton



CEFIXIME			
cefixime powder, for suspension			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68180-405
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
CEFIXIME (UNII: 971IC92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	100 mg in 5 mL	

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

Product Characteristics		
Color	WHITE (off-white to pale yellow)	Score
Shape		Size
Flavor	STRAWBERRY (Strawberry)	Imprint Code
Contains		

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-405-01	50 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/20/2015	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065129	04/20/2015	

CEFIXIME
cefixime powder, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68180-407
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
CEFIXIME (UNII: 971IC92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	200 mg in 5 mL

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

Product Characteristics		
Color	WHITE (Off White to Pale Yellow Powder)	Score
Shape		Size
Flavor	STRAWBERRY (Strawberry)	Imprint Code
Contains		

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-407-03	50 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/20/2015	
2	NDC:68180-407-04	75 mL in 1 BOTTLE; Type 0: Not a Combination Product	04/20/2015	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065355	04/20/2015	

CEFIXIME
cefixime capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68180-416
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
CEFIXIME (UNII: 971IC92E55) (CEFIXIME ANHYDROUS - UNII:XZ7BG04GJX)	CEFIXIME ANHYDROUS	400 mg

Inactive Ingredients	
Ingredient Name	Strength
CROSPROVIDONE (UNII: 2S7830E561)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN (UNII: 2G86Q327L)	
HYDROXYPROPYL CELLULOSE, LOW SUBSTITUTED (UNII: 2165RE0K14)	

MAGNESIUM STEARATE (UNII: 70097M6130)	
MANNITOL (UNII: 3OWL53L36A)	
POTASSIUM HYDROXIDE (UNII: WZHC48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FX9V2JF)	

Product Characteristics			
Color	PINK (Pink Opaque Cap) , PINK (Pink Opaque Body)	Score	no score
Shape	CAPSULE	Size	26 mm
Flavor		Imprint Code	LU;U43
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-416-11	1 in 1 CARTON	12/01/2018	
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:68180-416-08	50 in 1 BOTTLE; Type 0: Not a Combination Product	12/01/2018	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065129	12/01/2018	

Labeler - Lupin Pharmaceuticals, Inc. (089153071)

Registrant - LUPIN LIMITED (675923163)

Establishment			
Name	Address	ID/FEI	Business Operations
LUPIN LIMITED		725504448	MANUFACTURE(68180-405, 68180-407, 68180-416) , PACK(68180-405, 68180-407, 68180-416)

Revised: 11/2018

Lupin Pharmaceuticals, Inc.