

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**202091Orig1s000**

**MICROBIOLOGY REVIEW(S)**

## Division of Anti-Infective and Ophthalmology Products Clinical Microbiology Review

**NDA:** 202091, Cefixime for Oral Suspension, 100 mg/mL

Date Company Submitted: 25 October 2010  
Date received by CDER: 25 October 2010  
Date Assigned: 25 October 2010  
Date Completed: 26 April 2011  
Reviewer: Kerry Snow MS

**NAME AND ADDRESS OF APPLICANT:**

Lupin Pharmaceuticals, Inc.  
111 South Calvert Street, 21<sup>st</sup> Floor  
Baltimore, Maryland 21202

**CONTACT PERSON:**

Pramod Dahibhate, General Manager – Regulatory Affairs  
410-576-2000

**DRUG PRODUCT NAMES:**

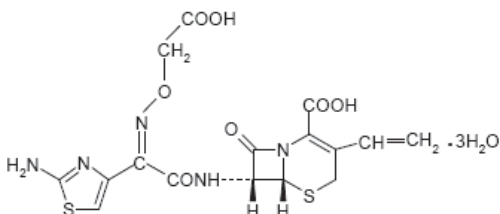
Proprietary Name: SUPRAX®

Code Name: none

Established Name: SUPRAX® Cefixime for Oral Suspension

Chemical Name: (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-(carboxymethyl) oxime] trihydrate.

**STRUCTURAL FORMULA:**



**MOLECULAR FORMULA:**

$\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}_7\text{S}_2 \cdot 3\text{H}_2\text{O}$

**MOLECULAR WEIGHT:**

507.50 as trihydrate

**PROPOSED DOSAGE FORM AND STRENGTH:**

Oral suspension; 100 mg/mL

**ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:**

Oral

**DISPENSED:**

Rx

**PROPOSED INDICATION:**

Uncomplicated UTIs caused by *Escherichia coli* and *Proteus mirabilis*; Otitis Media caused by *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis*, and *Streptococcus pyogenes*; Pharyngitis and Tonsillitis caused by *Streptococcus pyogenes*; (b) (4) AECB caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*; Uncomplicated Gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoeae*.

**RELATED DOCUMENTS:**

ANDA 065129; SUPRAX<sup>®</sup> Cefixime for Oral Suspension USP, 100 mg/5 mL (approved 10 April 2007)

ANDA 065130; SUPRAX<sup>®</sup> Cefixime Tablets, 400mg (approved 12 February 2004)

ANDA 065355; SUPRAX<sup>®</sup> Cefixime for Oral Suspension, 200 mg/5 mL (approved 10 April 2007)

ANDA 065380; SUPRAX<sup>®</sup> Cefixime Tablets (chewable), 100 mg, 150 mg, and 200 mg (approved 25 October 2010)

NDA 050621; SUPRAX<sup>®</sup> Cefixime Tablets, 200 mg and 400 mg (discontinued)

NDA 050622; SUPRAX<sup>®</sup> Cefixime for Oral Suspension, 100 mg/5mL (discontinued)

**TYPE OF SUBMISSION:**

New Drug Application [505(b)(2)]

**PURPOSE OF SUBMISSION:**

This Applicant is utilizing the 505(b)(2) regulatory pathway to seek approval of SUPRAX<sup>®</sup> Cefixime for Oral Suspension, 100 mg/mL. The RLD referenced in this application is SUPRAX<sup>®</sup> Cefixime for Oral Suspension, 200 mg/5 mL (ANDA 065355, Lupin Pharmaceuticals, Inc.).

**REMARKS:**

The Applicant is seeking approval for a new formulation of SUPRAX<sup>®</sup>, SUPRAX<sup>®</sup> Cefixime for Oral Suspension, 100 mg/mL. The submission includes data from two bioavailability/bioequivalence studies intended to establish a clinical bridge to the existing reference listed drug (SUPRAX<sup>®</sup> Cefixime for Oral Suspension, 200 mg/5mL). No new dosing regimen is proposed. No new microbiological studies have been undertaken, in support of this Application, and no microbiological data has been included for review.

**SUMMARY AND RECOMMENDATIONS:**

From the clinical microbiology perspective, this NDA submission may be approved.

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## EXECUTIVE SUMMARY

### I. IN VITRO INFORMATION

#### MECHANISM OF ACTION

Cefixime inhibits cell wall biosynthesis by binding transpeptidases in the cell wall, inhibiting cross-linkage of the terminal glycine residue to pentapeptide (D-alanine). Cefixime demonstrates high affinity binding of penicillin binding proteins (PBPs) 3, 1a, and 1b. Inhibition of cell wall biosynthesis results in rapid cell lysis. Cefixime is stable in the presence of many  $\beta$ -lactamases. The Applicant has provided no new data describing the mechanism of action of cefixime.

#### ANTIMICROBIAL SPECTRUM OF ACTIVITY

The Applicant has provided information from the published literature to describe the in vitro antibacterial activity of cefixime. The presented studies, as well as other data not provided by the Applicant, support the claim of activity against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Escherichia coli*, *Proteus mirabilis*, and *Neisseria gonorrhoeae* (although reports of decreased activity of cefixime against isolates of *N. gonorrhoeae* are noted). Activity of cefixime against isolates of *Streptococcus pneumoniae*, particularly isolates with reduced susceptibility to penicillin, is not supported by the data presented in this submission.

#### RESISTANCE STUDIES

No new information has been included in this submission, describing the mechanism of resistance to cefixime, or the occurrence of antimicrobial resistance in species of interest.

#### ANTIMICROBIAL INTERACTION STUDIES

The Applicant has provided no new information concerning the interaction of cefixime with other antibacterial drugs.

#### EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

The Applicant has provided no new information regarding the effects of miscellaneous factors on the antibacterial activity of cefixime.

#### BACTERICIDAL ACTIVITY

No new studies have been included in this submission that describe the bactericidal activity of cefixime.

### II. HUMAN AND ANIMAL STUDIES

#### ANIMAL DISEASE MODELS

No new animal efficacy studies were performed in support of this application.

#### PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The Applicant has submitted data from two clinical studies, Study 312-07 in adult subjects in fasting conditions and Study 313-07 of adult subjects in fed conditions, that demonstrate bioavailability/bioequivalence of cefixime 100 mg/mL oral suspension to the RLD (Suprax 200 mg/5 mL oral suspension).

### **III. CLINICAL TRIALS**

No new clinical trials were performed in support of this application.

### **IV. SUSCEPTIBILITY TEST METHODS**

The Applicant has included no new information in this submission, relevant to cefixime susceptibility testing procedures and methods.

## INTRODUCTION

Cefixime (FK027) is a third generation oral cephalosporin with bactericidal activity against several significant upper respiratory pathogens (including *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*), some members of the family Enterobacteriaceae (including *Escherichia coli* and *Proteus* species), and *Neisseria gonorrhoeae*.

Cefixime is currently marketed as a 200 mg/ 5 mL suspension, indicated for the treatment of uncomplicated urinary tract infections (caused by *E. coli* and *P. mirabilis*), otitis media (caused by *H. influenzae*, *M. catarrhalis*, and *S. pyogenes*), pharyngitis and tonsillitis (caused by *S. pyogenes*), (b) (4) acute exacerbations of chronic bronchitis (caused by *S. pneumoniae* and *H. influenzae*), and uncomplicated gonorrhea (caused by *N. gonorrhoeae*). Recommended dosing for adults is 400 mg/daily, usually divided into two 200 mg doses (every 12 hours). The recommended dose for children is 8 mg/kg/day of the suspension.

## IN VITRO INFORMATION

### MECHANISM OF ACTION

Cefixime inhibits cell wall biosynthesis by binding transpeptidases in the cell wall, inhibiting cross-linkage of the terminal glycine residue to pentapeptide (D-alanine). Cefixime demonstrates high affinity binding of penicillin binding proteins (PBPs) 3, 1a, and 1b. Inhibition of cell wall biosynthesis results in rapid cell lysis. Cefixime is stable in the presence of many  $\beta$ -lactamases. The Applicant has provided no new data describing the mechanism of action of cefixime.

### ANTIMICROBIAL SPECTRUM OF ACTIVITY

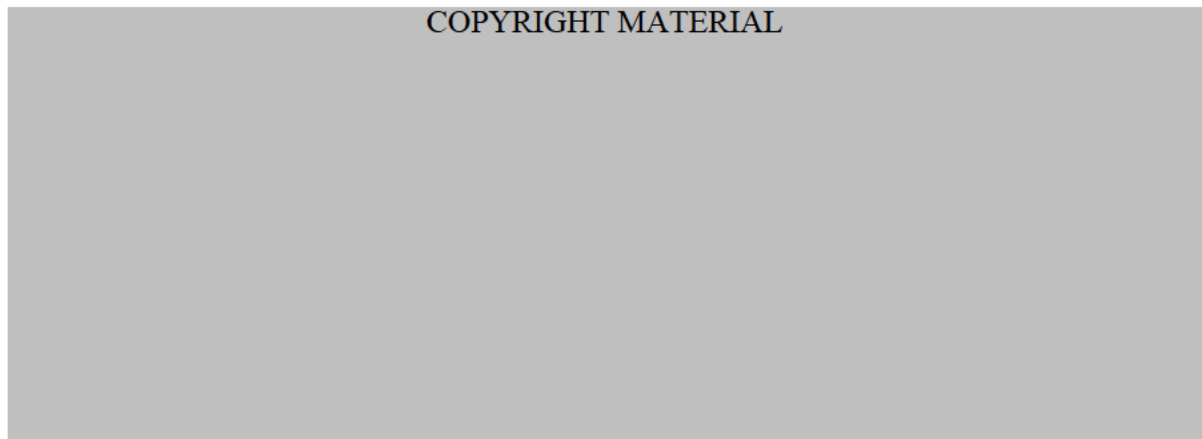
Cefixime is considered a Group IIIB oral cephalosporin, with broad spectrum activity against Gram negative pathogens but poor activity against *S. aureus* and *S. pneumoniae* [Bryskier 2005].

Upon request, the Applicant submitted a literature review, culling journal submissions that describe the in vitro antibacterial activity of cefixime. In general, the published literature supports the claim of antibacterial activity of cefixime against isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Streptococcus pyogenes*, and *Neisseria gonorrhoeae*. The literature does not support in vitro activity of cefixime against isolates of *Streptococcus pneumoniae*, particularly those isolates with reduced susceptibility to penicillin. Significant, recent publications are reviewed below.

In an investigation of commonly used "paediatric antibiotics for *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis* isolated from 2005 through 2007" [Harrison 2009], investigators determined the susceptibility of recently collected clinical isolates (from children up to 18 years old, with acute otitis media) to a variety of antimicrobials, including cefixime, using both CLSI and PK/PD breakpoints. PK/PD breakpoints were calculated using  $\%T > MIC$  as the target of attainment. MIC values were determined using methods approved by CLSI. BSAC (British Society for Antimicrobial Chemotherapy) breakpoints were used for determinations of *S. pneumoniae* susceptibility (no CLSI breakpoints are published for this drug-organism combination). The results of the investigation are summarized in Tables 1 through 4. While cefixime was active, in these studies, against isolates of *H. influenzae* (n=143, MIC<sub>90</sub> = 0.06 mcg/ml) and *M. catarrhalis* (n=62, MIC<sub>90</sub> = 0.25 mcg/ml), activity against isolates of *S. pneumoniae* was poor. Against all isolates of *S. pneumoniae* (n=208), the cefixime

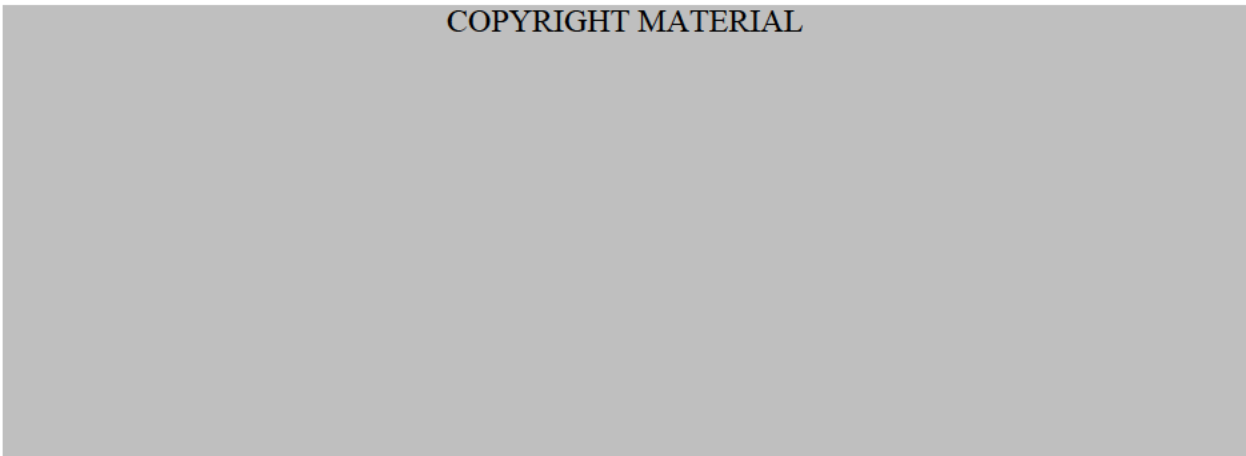
MIC<sub>90</sub> value was 16 mcg/mL (PK/PD % susceptible = 57.7). Against *S. pneumoniae*, serotype 19A isolates, the cefixime MIC<sub>90</sub> was > 16 mcg/mL (PK/PD % susceptible = 33.3).

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from: Harrison 2009

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from: Harrison 2009

(b) (4)

from: Harrison 2009

In another investigation [Perez-Vazquez 2003], researchers determined the antimicrobial activity of cefixime and comparators against isolates of *H. influenzae* with varying levels of susceptibility to ciprofloxacin (CIP). Susceptibility testing was performed using methods approved by CLSI, with appropriate quality control. The results of the study are summarized in Table 5. Cefixime was active against both groups of isolates, with MIC<sub>90</sub> values of 0.12 mcg/ml and 0.5 mcg/ml against Group I (CIP MIC ≤ 0.06 mcg/ml) and Group II (CIP MIC ≥ 0.12 mcg/ml) isolates, respectively.

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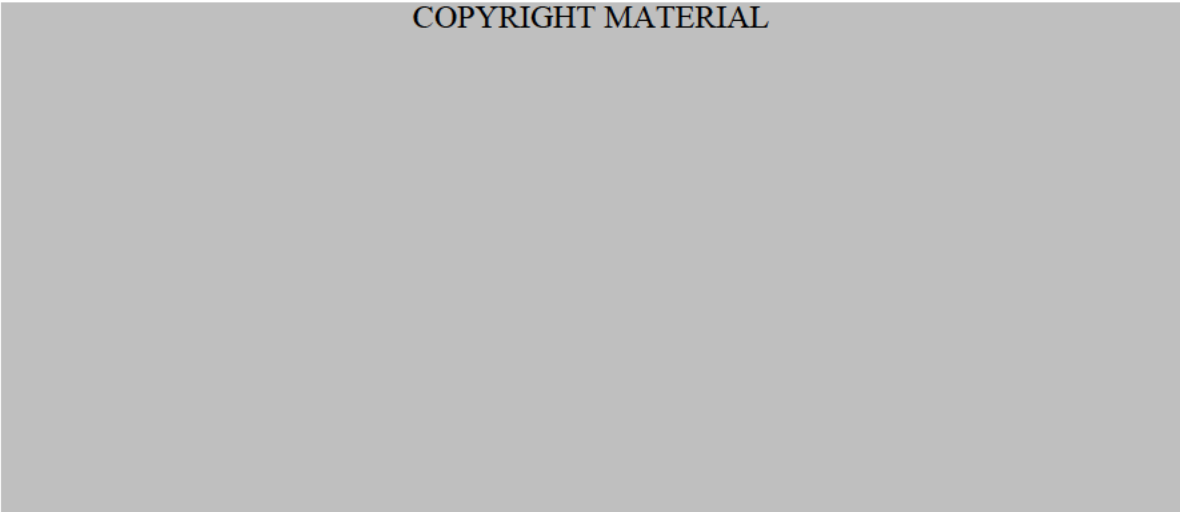
from: Perez-Vazquez 2003

In a study conducted in 2003 [Zhanel 2003], researchers investigated the activity of cefixime and comparators against clinical isolates of *H. influenzae* and *M. catarrhalis* collected from respiratory specimens, at 25 medical centers in Canada. Susceptibility testing was performed using methods approved by CLSI, with appropriate quality control. In this study, the MIC<sub>90</sub> values for *H. influenzae* (n=7566) and *M. catarrhalis* (n=2314) were ≤0.12 mcg/ml and 0.25 mcg/ml, respectively.

In a study conducted in 2002 [Schito 2002], investigators determined the susceptibility of various respiratory pathogens (including *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus*, and *K. pneumoniae*) collected in three European countries (Austria, Italy, and Spain), to cefixime and comparators. Susceptibility testing was performed using methods approved by

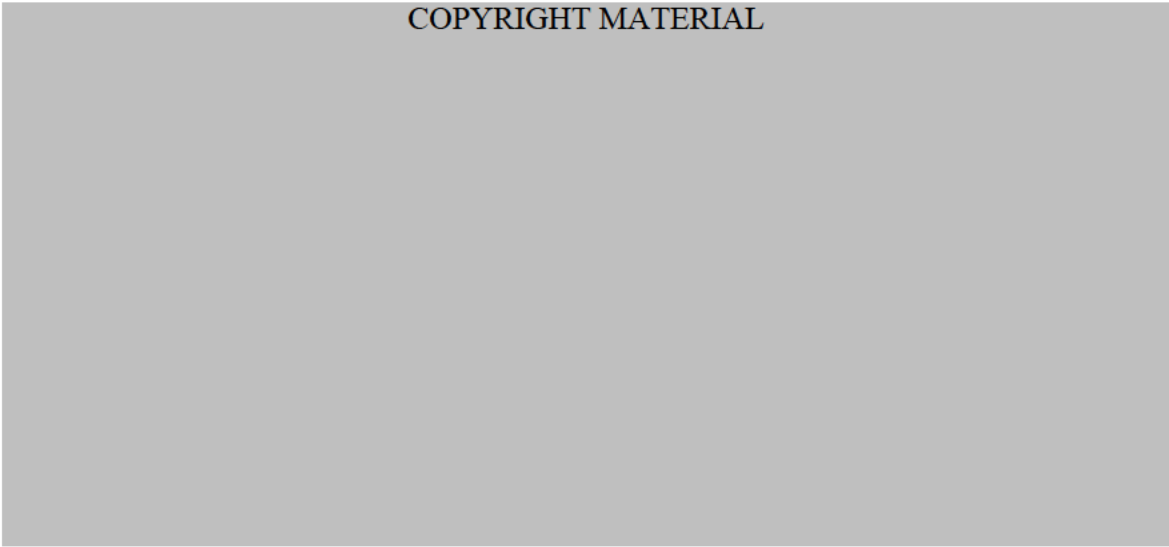
CLSI. Cefixime was active against isolates of *H. Haemophilus*, *M. catarrhalis*, *S. pyogenes*, and *K. pneumoniae*, but lacked activity against isolates of *S. pneumoniae* (particularly against penicillin-non-susceptible isolates) and *S. aureus*.

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from: Schito 2002

In a paper published in 2000 [Felmingham 2000], the Alexander Project reported susceptibility data for isolates collected worldwide (between 1996 and 1997), from community-acquired lower respiratory tract infections. The results of this study indicated a cefixime MIC<sub>90</sub> value of 32 mcg/ml against isolates of *S. pneumoniae* collected in 1997 (n = 2036). Against isolates of *H. influenzae* (n = 2721) and *M. catarrhalis* (n = 685) collected in 1997, the cefixime MIC<sub>90</sub> was 0.06 mcg/ml and 0.25 mcg/ml, respectively. The Alexander Project report published in 2003 [Jacobs 2003], which analyzed isolates collected between 1998 and 2000, indicates similar in vitro activity of cefixime against these three pathogens. The results of that study are summarized in Table 9.

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from: Jacobs 2003

A prospective study, performed in 1999 by Thornsberry et al. [Thornsberry 1999], reported similar in vitro activity against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, as that reported in the studies summarized above. Cefixime was active against isolates of *H. influenzae* and *M. catarrhalis*, with MIC<sub>90</sub> values of ≤ 0.25 mcg/ml and 0.5 mcg/ml, respectively, but

demonstrated poor activity against isolates of *S. pneumoniae* (MIC<sub>90</sub> >8mcg/ml).

The Applicant has submitted, in their review of recent literature, summaries of several studies describing the in vitro activity of cefixime against isolates of *Neisseria gonorrhoeae*. In a study published in 2004 [Heffernan 2004], investigators reported an MIC<sub>90</sub> value of 0.016 mcg/ml for cefixime against 413 isolates (range: 0.004-0.12 mcg/ml) isolated from patients in New Zealand in 2002.

In another study [Dorlencourt 2002], investigators in Kyrghyzstan tested 120 isolates of *N. gonorrhoeae* against cefixime and comparators, using “the reference agar dilution method”, and a susceptibility breakpoint of ≤ 1.0 mcg/ml (based on breakpoints published by the AntibioGramme Committee of the French Society for Microbiology; the CLSI susceptibility breakpoint for *N. gonorrhoeae* is ≤ 0.25 mcg/ml). The investigators determined that 98.3% of the tested isolates were “susceptible”, while 1.7% (n=2) fell in the intermediate range, with MIC values of 2.0 and 4.0 mcg/ml.

In a study performed in Surabaya, Indonesia [Joesoef 1994], investigators collected isolates from female sex workers and sent the organisms to the Centers for Disease Control (Atlanta, GA) for susceptibility testing. The cefixime MIC value for all tested isolates (n=86) was ≤ 0.125 mcg/ml.

More recent studies, not included in the Applicant’s summary, include reports of both reduced in vitro susceptibility of cefixime against isolates of *N. gonorrhoeae* [Allen 2011, Golparian 2010], as well as documented treatment failures [Unemo 2010, Yokoi 2007].

The Applicant has submitted summaries of studies conducted to describe the in vitro activity of cefixime against the Enterobacteriaceae. In a report from 1986, Fuchs et al [Fuchs 1986] described the in vitro activity of the “new orally absorbed cephalosporin.” In this study, the investigators reported that cefixime was active against isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Citrobacter diversus*, *C. amalonaticus*, *Proteus* species, *Providencia* species, *Serratia marcescens*, and *Salmonella enteritidis*. Activity was modest to poor against isolates of *Citrobacter freundii*, *Enterobacter* species, and *Morganella morganii*. Cefixime activity was also poor against isolates of *Pseudomonas* species, *Streptococcus pneumoniae*, *Staphylococcus* species, and *Bacteroides fragilis*. The investigators demonstrated that cefixime was resistant to hydrolysis by seven tested β-lactamases.

In another early investigation of the in vitro activity of cefixime against isolates from the family Enterobacteriaceae [Sanders 1989], researchers compared the in vitro antibacterial activity of cefixime to that of cefuroxime, cephalexin, and cefaclor, against Gram negative isolates with phenotypically defined β-lactamase activity. Overall, cefixime was more active than comparators against these isolates. The researchers concluded that only high levels of Class 1 β-lactamases were active against cefixime, and that cefixime was not a “strong inducer” of β-lactamase activity.

In a paper published in 1988, Knapp et al [Knapp 1988], investigators described similar activity of cefixime against members of the family Enterobacteriaceae as that described in the Fuchs paper, above. Cefixime was active against isolates of *E. coli*, *Klebsiella* species, *Proteus* species, *Providencia* species, and *Citrobacter diversus*, with MIC<sub>90</sub> values of ≤ 2.0 mcg/ml. Activity was poor against *Citrobacter freundii*, *Morganella morganii*, *Enterobacter* species, and *Pseudomonas aeruginosa*.

Studies performed since these early investigations (included in this submission), suggest that the profile for cefixime against members of the family Enterobacteriaceae remained relatively consistent into the 1990s [Sader 1993, Gerlach 1992]. Few surveillance studies have been performed since that time, involving cefixime against members of the family Enterobacteriaceae.

### **RESISTANCE STUDIES**

No new studies designed to investigate mechanisms of resistance to cefixime have been included in this submission.

### **ANTIMICROBIAL INTERACTION STUDIES**

No new in vitro studies designed to investigate interactions of cefixime with other antimicrobial drugs have been included in this submission.

### **EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY**

The Applicant has provided no new information regarding the effects of miscellaneous factors on the antibacterial activity of cefixime.

### **BACTERICIDAL ACTIVITY**

No new studies have been included in this submission that describe the bactericidal activity of cefixime.

## HUMAN AND ANIMAL STUDIES

### ANIMAL DISEASE MODELS

No new animal efficacy studies were performed in support of this application.

### PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The Applicant conducted two bioavailability/bioequivalence studies in support of this Application. The first, Study 312-07, was a “Phase 1, open-labeled, randomized, 2-treatment, 2-period, 2-sequence, single-dose, 2-way crossover study to compare the bioavailability and to characterize the pharmacokinetic profile of Cefixime 100 mg/mL Oral Suspension with respect to Suprax Cefixime 200 mg/5mL in healthy, adult subjects under fasting conditions and to assess bioequivalence. Findings of this study are summarized in Table 10. No significant differences between the RLD (Suprax 200 mg/5 mL) and the 100 mg/mL suspension were demonstrated.

**Table 10:** Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime under Fasting Conditions (N = 24)

| Parameters (Units)           | ln-transformed data            |                                  |                |                                      |
|------------------------------|--------------------------------|----------------------------------|----------------|--------------------------------------|
|                              | Geometric Least Squares Mean   |                                  |                | 90% Confidence Interval (Parametric) |
|                              | B: Cefixime 100 mg/mL (fasted) | A: Cefixime 200 mg/5 mL (fasted) | Ratio (B / A)% |                                      |
| C <sub>max</sub> (µg/mL)     | 3.636                          | 3.283                            | 110.8          | 104.23 – 117.71%                     |
| AUC <sub>0-t</sub> (µg*h/mL) | 29.736                         | 26.702                           | 111.4          | 103.97 – 119.29%                     |
| AUC <sub>0-∞</sub> (µg*h/mL) | 30.210                         | 27.284                           | 110.7          | 103.59 – 118.36%                     |

Source: Study 312-07 Final Report

The second investigation, Study 313-07, was a “Phase 1, open-label, randomized, 2-treatment, 2-period, 2-sequence, single dose, 2-way crossover study to compare the bioavailability and to characterize the pharmacokinetic profile of Cefixime 100 mg/mL Oral Suspension with respect to Suprax Cefixime 200 mg/5 mL in healthy, adult subjects under fed conditions and to assess the bioequivalence.” Findings of this study are summarized in Table 11. No significant differences between the RLD (Suprax 200 mg/5 mL) and the 100 mg/mL suspension were demonstrated.

**Table 11:** Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime under Fed Conditions (N = 24)

| Parameters (Units)           | (ln-transformed)<br>Geometric Least Squares Mean |                               |                | 90% Confidence Interval (Parametric) |
|------------------------------|--------------------------------------------------|-------------------------------|----------------|--------------------------------------|
|                              | B: Cefixime 100 mg/mL (fed)                      | A: Cefixime 200 mg/5 mL (fed) | Ratio (B / A)% |                                      |
| C <sub>max</sub> (µg/mL)     | 1.773                                            | 1.892                         | 93.7           | 84.48 - 103.88%                      |
| AUC <sub>0-t</sub> (µg*h/mL) | 14.531                                           | 15.375                        | 94.5           | 85.58 - 104.38%                      |
| AUC <sub>0-∞</sub> (µg*h/mL) | 15.088                                           | 15.897                        | 94.9           | 86.22 - 104.48%                      |

Source: Study 313-07 Final Report

## CLINICAL TRIALS

No new clinical trials were performed in support of this application.

## SUSCEPTIBILITY TEST METHODS

Cefixime is listed in the most recent version of "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement" [CLSI 2011], Table 1B, as a Group C Antimicrobial Agent ("Supplemental, Report Selectively") for infections involving *Haemophilus* species and *Neisseria gonorrhoeae*. The document includes cefixime among oral agents that may be used for empiric therapy for respiratory tract infections due to *Haemophilus* species, and states that susceptibility testing is not often useful for appropriate management of patients (but may be valuable for surveillance or epidemiological studies). The disk diffusion method is not approved for testing isolates of *Morganella* species. MIC testing of *Neisseria gonorrhoeae* must be performed using the agar dilution method (GC agar base and 1% defined growth supplement).

The Applicant has included no new information in this submission, relevant to cefixime susceptibility testing procedures and methods.

## APPLICANT'S PROPOSED SUBSECTION(S) OF THE PACKAGE INSERT

### 1 INDICATIONS AND USAGE

To reduce the development of drug resistant bacteria and maintain the effectiveness of cefixime and other antibacterial drugs, cefixime should be used only to treat or prevent 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 is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

#### 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* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive) and *Streptococcus pyogenes* (Efficacy for *Streptococcus pyogenes* in this organ system was studied in fewer than 10 infections).

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see CLINICAL STUDIES (14) section.

#### 1.3 Pharyngitis and Tonsillitis

Pharyngitis and Tonsillitis caused by *Streptococcus pyogenes*. (Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections, including the prophylaxis of rheumatic fever. (b) (4) is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, data establishing the efficacy of (b) (4) in the subsequent prevention of rheumatic fever (b) (4) not available.)

#### 1.4 (b) (4) Acute Exacerbations of Chronic Bronchitis

(b) (4) Acute Exacerbations of Chronic Bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (b) (4)

#### 1.5 Uncomplicated gonorrhea (cervical/urethral)

Uncomplicated gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing (b) (4)). (b) (4)

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

##### Microbiology

(b) (4), bactericidal action of cefixime results from inhibition of cell-wall synthesis. (b) (4)

Cefixime has been shown to be active against most (b) (4) of the following (b) (4) both in vitro and in clinical infections [see **INDICATIONS AND USAGE (1)**]:

Gram-positive (b) (4)  
*Streptococcus pneumoniae*,  
*Streptococcus pyogenes*.

Gram-negative (b) (4).  
*Haemophilus influenzae* (b) (4),  
*Moraxella* (b) (4) *catarrhalis* (most of which are beta-lactamase positive),  
*Escherichia coli*,  
*Proteus mirabilis*,  
*Neisseria gonorrhoeae* (b) (4).

(b) (4)

Gram-positive (b) (4)  
*Streptococcus agalactiae*.

Gram-negative (b) (4)  
*Haemophilus parainfluenzae* (b) (4)  
*Proteus vulgaris*,  
*Klebsiella pneumoniae*,  
*Klebsiella oxytoca*,  
*Pasteurella multocida*,  
*Providencia* species,  
*Salmonella* species,  
*Citrobacter amalonaticus*,  
*Citrobacter diversus*,  
*Serratia marcescens*.

(b) (4)

## Susceptibility Tests

### Diffusion Techniques

Quantitative methods that require measurement of zone diameters give an estimate of

(b) (4)

(b) (4)

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## REFERENCES

1. Allen VG, Farrell DJ, et al. Molecular analysis of antimicrobial resistance mechanisms in *Neisseria gonorrhoeae* isolates from Ontario, Canada. *Antimicrob Agents Chemother*. 2011; 55: 703-12.
2. Bryskier A, *Antimicrobial Agents: Antibacterials and Antifungals*. 2005. ASM Press. Washington, DC
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