

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203195Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Submission Number 203195  
Submission Code 000

Letter Date June 28, 2011  
Stamp Date August 01, 2011  
PDUFA Goal Date June 01, 2012

Reviewer Name Nasim Moledina, M.D.  
Review Completion Date April 30, 2012

Established Name Cefixime Capsules  
(Proposed) Trade Name Suprax<sup>®</sup>  
Therapeutic Class Cephalosporin  
Applicant Lupin Limited

Priority Designation S

Formulation Oral  
Dosing Regimen 400 mg capsule once daily  
Indication Uncomplicated UTI, pharyngitis  
and tonsillitis, AECB, and  
uncomplicated gonorrhea  
Intended Population Adults

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>3</b>
1.1	Recommendation on Regulatory Action .....	3
1.2	Risk Benefit Assessment .....	3
1.3	Recommendations for Postmarketing Risk Management Activities .....	3
1.4	Recommendations for other Post Marketing Study Commitments .....	3
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND.....</b>	<b>3</b>
2.1	Product Information.....	3
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>4</b>
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....</b>	<b>4</b>
4.1	Chemistry Manufacturing and Controls .....	4
4.2	Clinical Microbiology.....	5
4.3	Preclinical Pharmacology/Toxicology.....	5
4.4	Clinical Pharmacology .....	6
<b>5</b>	<b>SOURCES OF CLINICAL DATA .....</b>	<b>7</b>
5.1	Tables of Clinical Studies .....	7
5.2	Review Strategy.....	7
5.3	Discussion of Individual Studies .....	7
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>7</b>
6.1	Indication .....	8
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>8</b>
7.1	Methods .....	8
7.2	Adequacy of Safety Assessments .....	8
7.3	Major Safety Results .....	9
7.4	Supportive Safety Results.....	9
7.5	Other Safety Explorations .....	9
7.6	Additional Safety Explorations.....	9
7.7	Additional Submissions.....	9
<b>8</b>	<b>POSTMARKETING EXPERIENCE.....</b>	<b>9</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>9</b>
9.1	Literature Review/References .....	9
9.2	Labeling Recommendations .....	21
9.3	Advisory Committee Meeting .....	21

## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

To support the safety and efficacy of Suprax<sup>R</sup> Cefixime Capsules, 400 mg, the applicant conducted one (1) bioavailability/bioequivalence study to establish a clinical bridge to the RLD SUPRAX<sup>R</sup> Cefixime Tablets USP, 400 mg (ANDA# A065 130). There are no clinical studies submitted for review. Additional submissions were Suprax labeling (Lupin Pharma, 2008) and published literature articles.

Based on the review of the data submitted, the following recommendations are made by the Medical Officer, Dr. Nasim Moledina:

This is a 505(b)(2) NDA submission, where the applicant is relying on FDA's previous findings of safety and efficacy for Suprax (cefixime) tablets as the basis for approval of their capsule formulation. Based on the data submitted for one bioequivalence/bioavailability study and published literature articles in support of safety and efficacy of this product, this application is recommended for approval.

### **1.2 Risk Benefit Assessment**

Additional data to determine Risk Benefit assessment is not required at this time.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

No special risk management activity is required.

### **1.4 Recommendations for other Post Marketing Study Commitments**

None at this time.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Lupin Limited is seeking approval of a new formulation of Suprax<sup>®</sup> (cefixime) Capsules, 400mg. The sponsor is utilizing the 505(b)(2) regulatory pathway for the approval of Suprax<sup>®</sup> Cefixime Capsules, 400 mg. The reference listed drug (RLD) to support the safety and efficacy of the Lupin product is SUPRAX<sup>®</sup> Cefixime Tablets USP, 400 mg; ANDA# 065130, held by LUPIN PHARMS. This application also relies on FDA's previous findings of safety and efficacy for SUPRAX<sup>®</sup> cefixime 400 mg tablets, originally marketed by Lederle Laboratories under NDA 50-621. Lupin provided certification of no unexpired patents for both NDA 50621 and ANDA 065130 in this NDA application.

### 3 Ethics and Good Clinical Practices

This NDA has been submitted as a 505(b)(2) application. There were no clinical studies submitted, other than the bioequivalence/bioavailability study described in the clinical pharmacology review.

### 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

#### 4.1 Chemistry Manufacturing and Controls

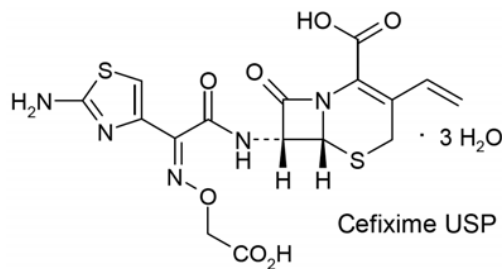
The Chemistry and Manufacturing Review was done by Maotang Zhou, Ph.D. His detailed review is in DARRTS dated April 17, 2012. Please refer to his review. A summary of the review is presented here:

**Chemical Name:** [6*R* -[6 $\alpha$  ,7 $\beta$  (*Z*)]-(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

**Molecular Formula:** C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>7</sub>S<sub>2</sub>·3H<sub>2</sub>O

**Molecular Weight:** 507.50

**Chemical Structure:**



#### Description of the Drug Product(s) and Drug Substance(s)

NDA 203-195 is a 505(b)(2) application submitted by Lupin Limited to seek approval of a new formulation of Suprax<sup>®</sup> (cefixime USP) Capsules, 400 mg. Currently the firm also markets the reference listed drug (RLD), Suprax<sup>®</sup> (cefixime USP) Tablets , 400 mg (ANDA #65130, held by Lupin Pharms).

#### Drug Substance

The drug substance is Cefixime, USP. Its empirical formula is C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>7</sub>S<sub>2</sub>·3H<sub>2</sub>O and molecular weight is 507.50. The drug substance, Cefixime USP is manufactured by Lupin

NDA 203195  
Suprax<sup>®</sup> 400 mg Capsules

Limited, in Mandideep, India and its CMC information is referred to DMF 15996. The holder DMF 15996 is also the applicant of NDA 203195. DMF 15996 is current and adequate.

## Drug Product

Suprax<sup>®</sup> (cefixime) Capsules, 400 mg are size “00EL” capsules with dark brown cap and dark brown body imprinted with “LU” on cap and “U43” on body in white ink containing white to yellowish white granular powder. All of the excipients in the new formulation are of USP/NF grade and can be found using FDA’s Inactive Ingredients Guide (IIG) Search for approved drug products at the same or higher amounts than the proposed drug product. The capsule shells meet acceptance specifications. The drug product will be manufactured by Lupin Limited at Madhya Pradesh, India. A [REDACTED]<sup>(b) (4)</sup> method is selected due to the [REDACTED]<sup>(b) (4)</sup> property of the drug substance.

The drug product specifications include description, identification, water content, dissolution, uniformity of dosage units, degradation products and assay, and microbial limits. The acceptance criteria are comparable to those of other FDA-approved cefixime formulations manufactured by the same applicant. The specifications have been [REDACTED]<sup>(b) (4)</sup> according to FDA’s recommendation during the NDA review and are deemed appropriate as revised.

The CMC reviewer recommended approval of the NDA. Overall, the CMC information as provided in the NDA is adequate to assure the identity, strength, purity and quality of the drug product.

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have “Acceptable” site recommendation. All labels have the required CMC information.

### 4.2 Clinical Microbiology

The microbiology reviewer for this application is Avery Goodwin. Please refer to his comments on the PLR labeling for this application. The review is in DARRTS dated 4/16/2012.

### 4.3 Preclinical Pharmacology/Toxicology

The toxicology reviewer is Amy Nostrandt. No new toxicology information has been submitted. Please refer to her comments on the PLR labeling for this application. The review is in DARRTS dated 10/3/2011.

#### 4.4 Clinical Pharmacology

The clinical Pharmacology review was conducted by Assadollah Noory, Ph.D. His review was still in draft at this writing. A summary of his review is presented here:

This application for cefixime 400 mg capsules includes one bioequivalence study report. Study LBC-10-044 was conducted under fasting conditions to assess the bioavailability of the capsule relative to the tablet (reference product); the capsule was also given with food to assess the effect of food on the capsule relative to the fasting conditions. The study was a randomized, open-label, balanced, analyst-blind, three-treatment, three-period, three-sequence, single-dose, crossover bioequivalence study assessing the bioequivalence between Suprax<sup>®</sup> capsules containing 400 mg cefixime by Lupin Inc. and Suprax<sup>®</sup> tablets (cefixime 400 mg) by Lupin Inc. in healthy adult subjects.

His conclusions were that the 90% confidence limits for cefixime are within 80% - 125% for AUC and C<sub>max</sub> indicating that the capsule is bioequivalent to tablet under fasting conditions. The results of study LBC-10-044 indicate that the Suprax<sup>®</sup> capsule provides acceptable exposure compared to Suprax<sup>®</sup> tablet under fasting conditions. However, food reduces cefixime exposure by 15% based on AUC and 25% based on C<sub>max</sub>. Also there is an increase in time to maximum concentration (T<sub>max</sub>) from 5.06 hours to 6.45 hours; approximately 27% increase.

#### **Clinical Pharmacology Recommendations:**

*The Office of Clinical Pharmacology completed the review of the clinical pharmacology portion of this NDA and finds that the sponsor has adequately addressed the clinical pharmacology aspects required for the approval of this NDA. Therefore, the Office of Clinical Pharmacology recommends the approval of the capsule formulation of Suprax<sup>®</sup>, NDA 203-195.*

The detailed ONDQA Biopharmaceutics Review conducted by Tien-Mien Chen, Ph.D. is in DARRTS dated 3/5/2012.

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution development report, the proposed dissolution method (submitted on 06/28/11), and the revised dissolution acceptance criterion (dated 02/08/12) for Suprax 400 mg capsules supporting the approval of this NDA.

The following recommendations have been made:

The proposed dissolution method and the revised dissolution criterion as shown below are acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Dissolution Medium	Acceptance Criterion
Type I (Basket)	100 rpm	900mL	37°C ± 0.5°C	0.05 M phosphate buffer, pH 7.2	Q = $\frac{Q}{Q_0}$ % at 45 min

NDA 203195  
Suprax<sup>®</sup> 400 mg Capsules

From the Biopharmaceutics perspective, 505(b)(2) NDA for Suprax (Cefixime) 400 mg capsules is recommended for approval.

## **5 Sources of Clinical Data**

Lupin Limited, hereforth designated as the Applicant, submitted an original New Drug Application (NDA) for its product, Suprax<sup>®</sup> (Cefixime) Capsules, 400 mg. The sponsor is utilizing the 505(b)(2) regulatory pathway for the approval of Suprax<sup>®</sup> Cefixime Capsules, 400 mg. The reference listed drug (RLD) to support the safety and efficacy of the Lupin product is SUPRAX<sup>®</sup> Cefixime Tablets USP, 400 mg; ANDA# A065130, held by LUPIN PHARMS.

The Applicant has marketed Suprax since the approval of SUPRAX<sup>®</sup> Cefixime Tablets USP, 400 mg on February 12, 2004 (ANDA# A065 130). Subsequently, it received approval for SUPRAX<sup>®</sup> Cefixime for Oral Suspension USP, 100 mg/5 mL, (approved on February 23, 2004; ANDA# A065 129), and SUPRAX<sup>®</sup> Cefixime for Oral Suspension USP, 200 mg/5 mL (approved on April 10, 2007; ANDA# A065355).

To support the safety and efficacy of Suprax<sup>R</sup> Cefixime Capsules, 400 mg, the applicant conducted one (1) bioavailability/bioequivalence study to establish a clinical bridge to the RLD SUPRAX<sup>R</sup> Cefixime Tablets USP, 400 mg (ANDA# A065 130). There are no clinical studies submitted for review.

The statistical review was conducted by Mark A. Gamalo, Ph.D. Please refer to his review in DARRTS dated 2/13/2012.

### 5.1 Tables of Clinical Studies

N/A

### 5.2 Review Strategy

Review of all the submitted literature articles was conducted.

### 5.3 Discussion of Individual Studies

N/A

## **6 Review of Efficacy**

### **Efficacy Summary**

In support of the 505(b)(2) NDA being submitted for cefixime 400 mg capsules, Lupin has conducted a bioavailability/bioequivalence clinical study to establish a clinical bridge to the RLD (Suprax<sup>®</sup> tablets, 400 mg) and also to assess the food effect on pharmacokinetics of cefixime capsules 400 mg. Lupin's cefixime 400 mg capsule was shown to be bioequivalent to Suprax



NDA 203195  
Suprax<sup>®</sup> 400 mg Capsules

tablet 400 mg when both were given at a dose of 400 mg cefixime to healthy adults under fasted (Study LBC-10-044) conditions. There was no significant difference in the rate and extent of absorption of cefixime from cefixime capsules when administered under fasted and fed conditions. Since the clinical bridge has been established, Lupin is relying on clinical efficacy and safety data from studies conducted in support of Suprax. For detailed review of the bioavailability/bioequivalence study, please refer to the review by Assad Noory dated 4/12/2012 in DARRTS.

No new clinical studies of the efficacy of cefixime were submitted for this NDA. The applicant has submitted several literature articles in support of efficacy and safety of Suprax 400 mg tablets. These are reviewed in section 9.1.

### 6.1 Indication

The proposed indications for Suprax (cefixime) capsules, 400 mg, were based on FDA's previous findings of safety and efficacy for cefixime oral products. The labeled indications include uncomplicated urinary tract infections, otitis media, pharyngitis and tonsillitis, acute exacerbations of chronic bronchitis, and uncomplicated gonorrhea. Of particular note, the labeling for acute exacerbation of chronic bronchitis (AECB) also included a claim for treatment of acute bronchitis. The review division proposed removal of the acute bronchitis claim, and the applicant agreed to the change in the label claim. As described in the literature, acute bronchitis is typically a viral infection, and there is no evidence that antibacterial treatment (whether cefixime or other antibacterials) is efficacious for this condition.

## 7 Review of Safety

### Safety Summary

The applicant has submitted several literature articles in support of efficacy and safety of Suprax 400 mg tablet. These are reviewed in section 9.1. No new clinical studies evaluating the safety and effectiveness of cefixime were submitted in this application; therefore, there is no new safety information in this section of the review.

#### 7.1 Methods

This section is N/A

#### 7.2 Adequacy of Safety Assessments

This section is N/A

NDA 203195  
Suprax<sup>®</sup> 400 mg Capsules

### 7.3 Major Safety Results

This section is N/A

### 7.4 Supportive Safety Results

This section is N/A

### 7.5 Other Safety Explorations

This section is N/A

### 7.6 Additional Safety Explorations

This section is N/A

### 7.7 Additional Submissions

None

## 8 Postmarketing Experience

While the capsule formulation has not been marketed yet, cefixime tablets have been marketed since 1986. Adverse reactions seen in postmarketing are described in the proposed labeling for Suprax (cefixime) capsules. The following section provides a summary of the literature for cefixime submitted by the applicant.

## 9 Appendices

### 9.1 Literature Review/References

#### **Review of references submitted by the applicant**

This review of literature articles in support of efficacy was conducted by Mr. James Blank. His review described findings from some of the literature references provided:

The applicant has included a list of the following references from the literature to support their request for approval of the application. A summary of each reference follows, along with the Clinical Reviewer's comments.

1. Asbach, H. W. 1991. Single dose oral administration of cefixime 400 mg in the treatment of acute uncomplicated cystitis and gonorrhea. *Drugs* 42 (Suppl. 4): 10-13.

The article describes the results of a placebo-controlled, randomized, double-blind study that evaluated the efficacy of cefixime as a 400 mg dose in 80 young women with acute lower urinary tract infections. Patients were randomly assigned to receive a single dose of either cefixime (400 mg), cotrimoxazole (160/800 mg), ofloxacin (200 mg), or placebo. Follow-up 14 to 17 days after treatment showed that among the patients who received cefixime or ofloxacin, 89.4% were successfully treated. In the cotrimoxazole treatment group, 84.2% were clinical successes, while 26.3% of the patients in the placebo group were clinical successes. Bacteriuria persisted in 8 patients in the antibiotic treatment groups, 5 of whom still complained of symptoms related to lower urinary tract infection. Among the 43 male patients with acute gonococcal urethritis, 100% were clinical cures after receiving a single 400 mg dose of cefixime. The author claims that single dose regimens offer the advantages of reduced expense, good tolerability, minimal alteration of normal bacterial flora, and the potential for improved patient compliance, compared with multiple dose antibacterial therapy.

**Clinical Reviewer's Comments:** *The results of the study show a single dose of cefixime 400 mg to be an effective antibacterial in the treatment of gonorrhea in men with a 100% cure rate and in most cases of uncomplicated urinary tract infections in women with an 89.4% cure rate. However, in other uncomplicated UTI studies with multiple doses of an antibacterial, higher cure rates are usually obtained. The author did not mention any adverse events that may have occurred in the study. The fact that treatment was a single dose of cefixime may be the reason for the absence of any reported adverse events.*

2. Barry, P.M. and J.D. Klausner. 2009. The use of cephalosporins for gonorrhea: The impending problem of resistance. *Expert Opin Pharmacother.* 10 (4):555-577.

This reference is a review article that discusses the problem of resistance to cephalosporin antibiotics in the treatment of gonorrhea. The gonococcus has repeatedly developed resistance to antimicrobials including sulfonamides, penicillin, tetracyclines, and fluoroquinolones. The only class of antibiotics recommended as first line therapy for gonorrhea in many regions are the third generation cephalosporins. Resistance to some third generation cephalosporins has recently been reported in Asia, Australia, and elsewhere. The mechanism of this resistance appears to be associated with a mosaic penicillin binding protein (pen A) in addition to other chromosomal mutations found to confer resistance to beta-lactam antibiotics (pen A, mtr R, pen B, pil Q). Cefixime is one of several oral cephalosporins with activity against *Neisseria gonorrhoeae*. A single oral dose of 400 mg of cefixime is recommended by the World Health Organization as first line therapy and the only oral regimen recommended in the United States.

**Clinical Reviewer's Comments:** *The review article discusses various aspects of gonorrhea, including the diagnosis, morbidity, epidemiology, and the use of different antibacterials for treatment. Cefixime was one of 7 oral cephalosporin antibacterials with activity against *N. gonorrhoeae*. The paper did not consider any safety issues associated with the different treatment regimens.*

3. Brogden, R.N. and D.M. Campoli-Richards. 1989. Cefixime A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 38 (4):524-550.

This reference is a review article that describes the antibacterial activity, pharmacokinetic properties, and the therapeutic potential of cefixime. The antibiotic is an orally active cephalosporin with a broad spectrum of activity against various species of pathogens including Enterobacteriaceae, *Hemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. It has little activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Cefixime is distinguished by its 3 hour elimination half-life which permits twice daily or in many instances once daily, administration. Comparative trials indicate that the efficacy of cefixime 200 to 400 mg daily is comparable with that of multiple daily doses of cotrimoxazole, amoxicillin or amoxicillin/clavulanic acid in treating uUTI, lower respiratory infections and acute tonsillitis or pharyngitis. The most frequently occurring adverse events are diarrhea and stool changes which are usually mild to moderate in severity.

**Clinical Reviewer's Comments:** *This article, as one of the older ones included, was published in 1989, not too long after cefixime was approved. The paper points out the long half-life of the drug compared to some other cephalosporin antibiotics on the market at the time. The review article did contain a section on adverse effects reported in patients treated with cefixime. The adverse events were regarded as transient, and mild to moderate in severity. Diarrhea and stool changes were the most frequently reported. The overall incidence of diarrhea was 13.8% in both populations of a study involving 1575 adults and 615 children. There was a tendency for a higher incidence with once daily than twice daily administration in adults (15.3% vs 10.3 %) but this trend was not apparent in children.*

4. Ho, M.W., F.D. Wang, C.P. Fung, et al. 2001. Comparative study of ceftibuten and cefixime in the treatment of complicated urinary tract infections. J. Microbiol. Immunol. Infect. 34:185..189.

The reference concerns a randomized, open-label, comparative study of ceftibuten and cefixime in the treatment of complicated UTI conducted in Taiwan. There were 62 patients initially enrolled in the study, with 17 excluded for various reasons. The remaining 45 patients were divided with 23 receiving ceftibuten (200 mg twice daily) and 22 receiving cefixime (200 mg twice daily). The clinical efficacy rate was 78.3% among the ceftibuten treatment group compared to 77.3% for the cefixime treatment group. The bacteriological eradication rate was 52.2% for the ceftibuten group versus 63.6% for the cefixime group. Adverse events reported among the ceftibuten group included diarrhea and slight elevation of liver transaminases in two (6.5%) patients. Among the cefixime treated group, adverse events included slight elevation of liver transaminase in two (6.5%) patients and skin rash in one (3.2%) patient. The results suggest that ceftibuten and cefixime are comparable, given 200 mg twice daily, in the treatment of complicated urinary tract infections.

**Clinical Reviewer's Comments:** *The paper reports the results of a small, foreign study that show cefixime and ceftibuten to be comparable in the treatment of complicated urinary tract infections. Adverse events caused by cefixime treatment included slight elevation of serum level of liver transaminases in two patients (6.5%) and skin rash in one patient (3.2%). All of these adverse events resolved quickly after the regimen had been completed, and no patient discontinued the regimen because of the adverse effects.*

5. Hook, E.W., W.M. McCormack, D. Martin, et al. 1997. Comparison of single-dose oral grepafloxacin with cefixime for treatment of uncomplicated gonorrhea in men. *Antimicrob. Agents Chemother.* 41:1843-1845.

The study reported in this reference compares the safety and efficacy of a single oral dose of grepafloxacin with those of cefixime in the treatment of uncomplicated gonorrhea in men. The study enrolled 351 male patients with uncomplicated gonorrhea. The patients were randomized to receive either a single dose of grepafloxacin (400 mg) or cefixime (400 mg). Of the 351 patients in the study, 149 in the grepafloxacin-treatment group and 150 in the cefixime-treatment group were microbiologically evaluable. *Neisseria gonorrhoeae* was eradicated from the urethra in 99% of the grepafloxacin treatment group and in 97% of the cefixime-treatment group. Eradication rates for both regimens were 100% in the 16% (47/299) of patients who were infected with penicillin-resistant *N. gonorrhoeae* and 97% in the 21% (62/299) of patients infected with tetracycline-resistant strains.

**Clinical Reviewer's Comments:** *Single dose cefixime and grepafloxacin both appear to be very safe and effective in eradication of isolates of N. gonorrhoeae. The most common adverse events among patients receiving cefixime were headache (3%) and nausea (2%).*

6. Kiani, R., D. Johnson, and B. Nelson. 1988. Comparative, multicenter studies of cefixime and amoxicillin in the treatment of respiratory tract infections. *Amer. J. Med.* 85 (Suppl. 3A):6-13.

This publication discusses the results of two multi-center studies which compared cefixime to amoxicillin in the treatment of lower respiratory tract infections (LRTI) and upper respiratory tract infections (URTI). A total of 560 patients were enrolled, with 244 patients in the LRTI group and 316 patients in the URTI group. A 400 mg dose of cefixime was given once a day, while amoxicillin (250 or 500 mg) was administered three times daily. The duration of therapy was 14 days for both treatment groups. Eighty percent of the patients in the LRTI group had acute bronchitis caused most frequently by *S. pneumoniae* (13%), *H influenzae* (28%), and *E. coli* (10%). A favorable clinical response was obtained by 100% of the cefixime treated patients (22/22) and in 96% of the amoxicillin-treated patients (23/24). Bacterial eradication rates were 100% and 83% for cefixime and amoxicillin, respectively. In the URTI group, 80% of the patients had pharyngitis and 14% were treated for tonsillitis. The most frequently isolated pathogens were Group A, beta-hemolytic streptococcus (69%) and *H influenzae* (8%). A favorable clinical response was obtained in 99% of the evaluable cefixime-treated group (n = 73) and in 98% of the amoxicillin-treated group (n = 66). The bacteriological eradication rates were 93% and 100%, respectively. The adverse events reported during both studies were similar in nature and frequency to those reported for the beta-lactam class of antibiotics.

**Clinical Reviewer's Comments:** *The reference describes another study involving 560 patients in which both cefixime and amoxicillin are shown to be effective in treating respiratory tract infections. The adverse experiences reported during both studies were similar in nature and frequency to those reported for other beta-lactam antibiotics with the exception of a higher incidence of diarrhea and stool changes with both drugs. In the LRTI study, the overall incidence*

*of adverse experiences was 43.4% (53 of 122) for cefixime-treated patients, and 47.5% (58 of 122) for amoxicillin-treated patients.*

7. Lorenz, J., P. Steinfeld, L. Drath et al. 1998. Efficacy and tolerability of 5- vs 10-day cefixime therapy in acute exacerbations of chronic bronchitis. Clin. Drug Invest. 15 (1):13-20.

The study reported in the above reference was a controlled trial that compared a 5-day regimen of cefixime (400 mg/day) with a 10-day regimen, also 400 mg/day. A total of 222 patients with acute exacerbations of chronic bronchitis (AECB) were enrolled and randomized into the two groups. There were 167 patients evaluable for efficacy analysis on a per-protocol basis. A successful clinical response was achieved in 91 % of the 5-day treatment group and in 89% of the 10-day treatment group. The bacteriological eradication rate was similar for both groups. More patients in the 10-day group reported an adverse event compared to the 5-day group, (19 versus 14%). The authors conclude that 400 mg once daily oral cefixime is an effective treatment for AECB and that the clinical efficacy of short-term (5-day) therapy is similar to that of standard (10-day) therapy.

**Clinical Reviewer's Comments:** *It is interesting that the results show the 5-day regimen to be as successful as the 10-day regimen. For example, at the 11 day evaluation, the 5-day-treatment outperformed the 10-day-treatment, 91% to 89%. At the 30-day evaluation, both treatment regimens showed similar success rates, 89% to 90%. Forty-three patients (19%) prematurely discontinued treatment (5-day, n=18; 10-day, n=25); the most common reason being the occurrence of an adverse event (12 and 11 patients, respectively).*

8. Low, D.E. 1995. Assessment of the use of cefixime for switch therapy. Infection, 23 (Suppl. 2):S91-S94.

The article discusses the possible use of cefixime as an agent amenable to switch therapy, this is the switch from a parenteral to an oral antimicrobial agent. The paper states that respiratory tract infections are the most commonly encountered infections in the USA. One of the advantages of switch therapy is a significant cost savings. A second important benefit derived from oral antibiotic therapy is the removal of intravenous catheters, which are a major source of nosocomial bacteremias. The author describes the properties, including pharmacokinetics, of cefixime and compares it to cefotaxime and ceftriaxone. It has a prolonged half-life, allowing for once a day dosing and has excellent tissue penetration. However, one problem with cefixime is its lack of coverage for *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*.

9. Ludwig, E. 1998. Cefixime in the treatment of respiratory and urinary tract infections. Chemother. 44 (suppl 1 ):31-34.

This reference describes a foreign study conducted in several countries located in Central and Eastern Europe. It was a Phase 4, open, non-randomized trial that utilized once daily cefixime in the treatment of acute sinusitis, acute otitis media, AECB, and pneumonia. In 45 children with acute sinusitis and 50 with acute otitis media, once-daily cefixime in a suspension (8 mg/kg) resulted in clinical cure or improvement in 45 (100%) and 48 (96%) patients, respectively. In 60

adult patients with acute exacerbations of chronic bronchitis and 12 with pneumonia, cefixime 400 mg resulted in cure or improvement in 59 (98%) and 12 (100%) patients, respectively. Also, the drug performed well in patients with urinary tract infections with cure in 80 (94%) patients, improvement in 4 (5%), and failure in 1 (1 %). Pathogens were eradicated in 35 of 36 children, including isolates of all *S. pneumoniae*, 40 of 45 patients with respiratory tract infections, and 64 of 71 isolates from patients with urinary tract infections.

**Clinical Reviewer's Comments:** *The results of this foreign study show cefixime to be effective in treating respiratory infections and urinary tract infection. Specific adverse events were not discussed in the paper. The author states that the rate of adverse events (4-5%) was relatively low in comparison with other studies. No other details were given.*

10. Markham, A. and R.N. Brogden. 1995. Cefixime A review of its therapeutic efficacy in lower respiratory tract infections. **Drugs** 49 (6):1007-1022.

This reference is a review article of cefixime that describes its *in vitro* antibacterial activity, pharmacokinetic properties, therapeutic use in several indications, tolerability, dosage and administration, and its role in the treatment of lower respiratory tract infections. Cefixime is active against such pathogens as *H influenzae*, *M catarrhalis*, and penicillin-susceptible *S. pneumoniae*, but inactive against *S. aureus*. The drug has a long elimination half-life (3 hours compared to 0.5 hours for cefaclor and 1.5 hours for cefalexin), which allows for once daily administration. In several comparative trials, cefixime had similar efficacy to amoxicillin± clavulanic acid, cefaclor, cefalexin, cefuroxime, and clarithromycin. As with other cephalosporin antibiotics, gastrointestinal disturbances are the most frequently reported adverse events in patients taking cefixime. Cases of pseudomembranous colitis have been reported. Numerous trials have evaluated the efficacy of cefixime as treatment for lower respiratory tract infection (LRTI). In a large non-comparative, multi-center trial in patients with acute bronchitis or acute exacerbations of chronic bronchitis, cefixime had a cure/improvement rate of 96.0%. Similar studies in patients with community-acquired LRTI have also shown cefixime to be clinically efficacious. In these studies, cefixime has been shown to be as effective as clarithromycin in adults and amoxicillin/clavulanic acid in children. Several comparative studies have shown that the rate of adverse events among patients taking cefixime was very similar to that in patients who received the comparator drug. Gastrointestinal symptoms, especially diarrhea, are the most frequent adverse events reported in patients treated with cefixime. The recommended adult dose is 400 mg/day which may be given as a single daily dose or 200 mg every 12 hours. The recommended dosage for children ≤ 12 years of age or weighing ≤ 40 kg is 8 mg/kg/day as an oral suspension. It may also be administered as a single daily dose or 4 mg/kg every 12 hours.

11. Mathews, B.L., R.I. Kohut, D.R. Edelstein, et al. 1993. Evaluation of cefixime in the treatment of bacterial maxillary sinusitis. *Southern Med. J.* 86 (3):329-333.

The results of a multi-center, non-comparative trial of cefixime in the treatment of acute sinusitis and acute exacerbation of chronic sinusitis are reported in this article. There were 118 adult patients enrolled at 6 hospitals or medical centers. Each patient received a single daily dose of 400 mg of cefixime for a mean duration of 10 days. For the 106 patients who completed a course

of therapy, 90% were either cured (61%) or showed improvement (29%). Among patients evaluated again 2 weeks after therapy, 91 % had a sustained clinical cure or improvement. The most common pathogens isolated in sinus exudates specimens obtained prior to therapy were *H. influenzae*, alpha-hemolytic streptococci, and *S. pneumoniae*. Twenty percent of the patients reported diarrhea.

**Clinical Reviewer's Comments:** *Diarrhea and loose stools were the most common adverse events, with an overall incidence of 20% (24 patients) and 8% (9 patients), respectively. Three patients discontinued therapy because of adverse events; one reported diarrhea, one diarrhea with nausea and vomiting, and one diarrhea and increased urination. These patients all recovered after stopping cefixime therapy.*

12. Megran, D.W., K. Lefebvre, V. Wilets, et al. 1990. Single-dose oral cefixime versus amoxicillin plus probenecid for the treatment of uncomplicated gonorrhea in men. *Antimicrob. Agents Chemother.* 34 (2):355-357.

The paper describes the results of a randomized, comparative study involving cefixime versus amoxicillin plus probenecid in the treatment of uncomplicated gonorrhea in men. A total of 170 men were enrolled in the study. Patients were randomized in a 2:1 ratio to receive either cefixime (800 mg in four 200 mg capsules) as a single oral dose (without probenecid) or amoxicillin (3.0 grams) and probenecid (1.0 gram) orally. The men were requested to return for a follow-up examination 6 to 9 days after treatment. In the cefixime treatment group, 96 of 97 (99%) men with urethritis were cured, while in the amoxicillin plus probenecid treatment group, 44 of 46 (96%) men with urethritis were cured. Both regimens were ineffective against coexistent infections with *Chlamydia trachomatis* and *Ureaplasma urealyticum*. In men with gonococcal urethritis, *C. trachomatis* was recovered at the initial visit or follow-up visit in 23 (24%) of 97 males given cefixime and 14 (30%) of 46 amoxicillin-treated patients. A total of 17 cefixime treated men and 18 who received amoxicillin were *U. urealyticum* positive before therapy.

**Clinical Reviewer's Comments:** *Since neither cefixime or amoxicillin are active against C. trachomatis or U. urealyticum, both antibiotics should be administered along with either tetracycline or another agent active against both pathogens. Side effects were common with both treatment regimens and occurred in 31 % of cefixime-treated men and in 30% of amoxicillin-treated men. All adverse events were mild and resolved spontaneously. The most common complaints were lower gastrointestinal in nature, and included diarrhea, loose stools, and cramping abdominal pain.*

13. Miler, J.M. 1997. Open study of the safety and efficacy of a single oral dose of cefixime for the treatment of gonorrhea in pregnancy. *Infect. Dis. Obstetr. Gynecol.* 5:259-261.

The reference is a report of a retrospective review of clinical records over a three-year period to evaluate the safety and efficacy of using a single 400 mg dose of cefixime in the treatment of gonorrhea during pregnancy. A total of 102 pregnant women, with a positive gonorrheal screen were treated with a single 400 mg dose of cefixime. Patients were evaluated approximately 2 weeks after treatment. A cure rate of 95.2% was found. Two patients, who also received



azithromycin, reported nausea and vomiting, while a third patient had diarrhea. Limited information was provided to describe outcomes in infants of women treated with cefixime during pregnancy, but did not describe any specific adverse outcomes.

**Clinical Reviewer's Comments:** *The retrospective study showed cefixime to be a safe, effective treatment for gonorrhea during pregnancy.*

14. Neu, H.C. and T.W. Chick. 1993. Efficacy and safety of clarithromycin compared to cefixime as outpatient treatment of lower respiratory tract infections. *Chest* 104: 1393-1399.

The reference describes the results of a randomized, double-blind, multi-center study that compared clarithromycin to cefixime in treating patients with community-acquired lower respiratory tract infections (CA-LRTI). There were 213 patients enrolled in the trial conducted by 23 investigators in the United States. Patients received either 500 mg of clarithromycin twice daily (n=103) or 400 mg of cefixime once daily (n=110) for 7 to 14 days. Among patients with bacterial pneumonia, 19% received clarithromycin and 21% received cefixime. Among patients with acute bacterial exacerbation of chronic bronchitis or asthmatic bronchitis, 81% received clarithromycin and 79% received cefixime. There was a cure or improvement among 86% of the patients treated with clarithromycin and 88% of the cefixime-treated patients. When only patients infected with *H. influenzae*, *M. catarrhalis*, or *S. pneumoniae* were evaluated, the clinical success rates were 97% for clarithromycin and 96% for cefixime. The bacterial eradication rate was 91% for clarithromycin and 90% for cefixime. Cefixime successfully eradicated all *H. influenzae* (n=23), but failed to eliminate *M. catarrhalis* in one case (15/16, 94%) and *S. pneumoniae* in 4 cases (8/12, 67%).

**Clinical Reviewer's Comments:** *The results of the study are consistent with the results from other studies in that cefixime is not as effective in eradication of *S. pneumoniae* compared to *H. influenzae* and *M. catarrhalis*. Adverse events occurred in 29% (30/103) of the clarithromycin-treated patients and in 23% (25/110) of the cefixime-treated patients. Eighteen patients in each treatment group ended the study early. Adverse events accounted for 8 patients in the cefixime-treated group. Again, the most frequent adverse events in both groups were related to the digestive system. Diarrhea and nausea were the most common complaints in the cefixime-treated group, 8 reports and 6 cases, respectively.*

15. Raz, R., E. Rottensterich, Y. Leshem, et al. 1994. Double-blind study comparing 3-day regimens of cefixime and ofloxacin in treatment of uncomplicated urinary tract infections in women. *Anticomb. Agents Chemother.* 38(5):1176-1177.

The reference describes the results of a study that compared 3-day regimens of cefixime and ofloxacin in the treatment of uncomplicated urinary tract infections in women. The double-blind, randomized study included a total of 105 women, with 54 receiving cefixime (400 mg once daily) and 52 receiving ofloxacin (200 mg twice a day). The respective clinical cure rates for the two groups of women were 89 and 92% after 7 days and 81 and 84% after 4 weeks. The respective microbiological cure rates (free of bacteriuria) for the two groups of women were 83 and 86% after 7 days and 77 and 80% after 28 days. The authors conclude that a 3-day cefixime

regimen appears to be as efficient as a 3-day ofloxacin regimen in the treatment of uncomplicated cystitis in women.

**Clinical Reviewer's Comments:** *The clinical cure rates and microbiological cure rates for the 2 regimens are very similar with slight differences of 2 to 3% in the cure rates. Because the numbers of women enrolled in the study were so small, there were no statistical evaluations conducted.*

16. Salvarezza, C.R., H. Mingrone, H. Fachinell, et al. 1998. Comparison of roxithromycin with cefixime in the treatment of adults with community-acquired pneumonia. *J. Antimicrob. Chemother.* 41 (Suppl. B):75-80.

The reference describes the results of an open, randomized study that compared the efficacy and tolerability of once daily dosing with either roxithromycin (300 mg) or cefixime (400 mg) for 8-10 days in the treatment of uncomplicated community-acquired pneumonia (CAP) in 3 outpatient clinics in Argentina. Sixty patients were enrolled with 17 males and 13 females receiving roxithromycin and 22 males and 13 females receiving cefixime. The most common pathogen isolated from the sputum was *Streptococcus pneumoniae* in 26 (43%) of the 60 patients. *Staphylococcus aureus*, *Hemophilus influenzae*, and *Moraxella catarrhalis* were isolated from 11 patients, while 7 patients in the roxithromycin group and 3 in the cefixime group had atypical pathogens that were detected by serology. At the end of the study, the clinical cure rates were 30/30 (100%) for the roxithromycin group and 28/30 (94%) for the cefixime group. One of the patients on cefixime was classified as a partial responder and one patient with a *Pseudomonas aeruginosa* infection was classified as a failure.

**Clinical Reviewer's Comments:** *The results of the study show cefixime to be an effective antimicrobial agent in the treatment of CAP caused by susceptible pathogens.*

**Medical Officer's Comments:** *Roxithromycin is not approved for marketing in USA.*

17. Verghese, A., D. Roberson, J.H. Kalbfleisch, et al. 1990. Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. *Antimicrob. Agents Chemother.* 34 (6):1041-1044.

The reference reports the results of a study that compared cefixime to cephalexin in the treatment of patients with acute bacterial exacerbations of chronic bronchitis (ABECB). Male patients were randomized to receive either cefixime at 400 mg daily or cephalexin at 250 mg every 6 hours for 14 days. Of the 130 patients enrolled, 86 were evaluable, with 38 in the cephalexin-treatment group and 48 in the cefixime-treatment group. There were 70.8% of cures in the cefixime-treatment group compared to 50% of cures in the group treated with cephalexin ( $p < 0.05$ ). When the categories of cured and improved were combined, no significant difference was noted between treatment groups (95.8% for cefixime versus 84.2% for cephalexin  $p = 0.06$ ), according to the authors. The two most common pathogens causing the ABECB were *H. influenzae* (33.7%) and *M. catarrhalis* (31.4%), accounting for over 60% of the cases. The third largest category was a mixed group in which more than one pathogen was recovered. *H. influenzae* and

*M. catarrhalis* were also predominant in this mixed group (15 patients). Overall, 37% of all *M. catarrhalis* isolates and 14% of all *H. influenzae* isolates produced  $\beta$ -lactamase. The most common adverse event was diarrhea noted in 6 patients in the cefixime treatment group and none in the cephalixin-treatment group.

**Clinical Reviewer's Comments:** *The combining of the number of patients cured with those that improved and the statement that there is no significant difference between the two treatment groups is questionable. The success rate for the cefixime-treated group was 95.8% compared to the success rate for the cephalixin group at 84.2% with a P value of 0.06. It doesn't seem as though the two treatment groups are equal. Six patients (9.2%) in the group treated with cefixime developed diarrhea, while no patients with cephalixin experienced this adverse event. Overall, the occurrence of side effects was more common in the group treated with cefixime when compared with that in the group treated with cephalixin (19 versus 5 episodes, respectively).*

## SAFETY

### Published Literature

Eleven studies from the published literature provide safety information for cefixime. Three other studies are referenced that provide information only on exposure of cefixime (no safety data reported). A review of the published literature for studies showing safety data for cefixime identified the following:

- Two randomized clinical studies evaluating cefixime for urinary tract infections (UTI)
- Six clinical studies (4 randomized and 1 non-comparative) evaluating cefixime for respiratory tract infections (RTI)
- Three clinical studies (2 randomized and 1 retrospective review) evaluating cefixime for uncomplicated gonorrhea

### Urinary Tract Infections (UTI)

Ho et al. (Ho, 2001) conducted a randomized, prospective, open-label trial to compare the clinical and microbiological efficacy and safety of ceftibuten and cefixime in the treatment of complicated UTI. Patients were randomly assigned to receive oral cefixime capsules 200 mg bid (N = 22) or oral ceftibuten capsules 200 mg bid (N = 23) for 10 – 14 days. AEs caused by ceftibuten treatment included diarrhea and slight elevation of the serum level of liver transaminase in 2 (6.5%) patients. AEs caused by cefixime treatment included slight elevation of serum level of liver transaminase in 2 (6.5%) patients and skin rash in 1 (3.2%) patient. All of these AEs resolved quickly after the regimen had been completed, and no patient discontinued the regimen because of the AEs. The authors concluded that both ceftibuten and cefixime, at 200 mg bid, are effective and safe in the treatment of complicated UTI.

### **Respiratory Tract Infections (RTI)**

Lorenz et al. (Lorenz, 1998) conducted a multicentre, double-blind, randomized, controlled clinical trial to compare the efficacy and tolerability of cefixime 400 mg once daily as a 5-day regimen versus a 10-day regimen in the treatment of acute exacerbations of chronic bronchitis (AECB). Patients were randomly assigned to receive oral cefixime 400 mg qd for 5 days (N = 110) or oral cefixime 400 mg qd for 10 days (N = 111). Among AEs at least possibly related to the study medication, gastrointestinal disorders, primarily mild or moderate diarrhea, were the most frequent. During active treatment, 13% of patients in the 5-day group and 18% in the 10-day group reported at least 1 AE related to gastrointestinal system. The difference in the AEs in the 2 treatment groups was not statistically significant. One patient died during the study from an extended carcinoma of the gall bladder and sigma that was undiagnosed at study entry. Seven patients experienced at least 1 serious AE, but in each case the relationship to the study medication was considered remote. One patient in the 10-day group developed severe and long lasting diarrhea 1 month after the completion of therapy; pseudomembranous colitis was excluded. Forty-three patients (19%) prematurely discontinued treatment (5-day, n = 18; 10-day, n = 25), the most common reason being the occurrence of an AE (12 and 11 patients, respectively). Two patients in the 10-day arm discontinued treatment because of therapeutic failure. There were no clinically significant changes in any of the laboratory tolerability parameters measured at baseline and at follow-up. The authors concluded that oral cefixime 400 mg once daily is an effective and well-tolerated treatment for AECB.

Matthews et al. (Matthews, 1993) conducted a multicentre, non-comparative trial of cefixime efficacy and safety in the treatment of acute sinusitis and acute exacerbation of chronic sinusitis. Adult patients with acute sinusitis or acute exacerbation of chronic sinusitis were administered cefixime 400 mg tablet qd (N = 118) for 10 - 14 days. The most frequently reported AEs were gastrointestinal, with 20% of patients reporting diarrhea. Three patients discontinued therapy because of side effects. The authors concluded that cefixime was effective in the treatment of bacterial sinus infections in adults and was well-tolerated.

To compare the efficacy and safety of clarithromycin with cefixime in the outpatient treatment of lower RTI, a multicentre, double-blind, randomized clinical trial was conducted by Neu et al. (Neu, 1993). Patients with lower RTI were randomly assigned to receive oral cefixime 400 mg qd (N = 110) or oral clarithromycin 500 mg bid (N = 103), for 7 - 14 days. The most frequent AEs in both groups were related to the digestive system. Nausea was the most common gastrointestinal complaint in the clarithromycin group (11 cases) and the second most common complaint in the cefixime group (6 cases), following diarrhea (8 cases in cefixime group; 2 in clarithromycin group). The only statistically significant difference in AEs was the high incidence of taste perversion, which was reported by 14 in clarithromycin group and 2 in cefixime group (p = 0.001). There was 1 death in clarithromycin group.

Verghese et al. (Verghese, 1990) conducted a randomized comparative study to compare the effects of cefixime against those of cephalexin in the treatment of acute bacterial bronchitis. Patients were randomly assigned to receive oral cefixime 400 mg qd (N = 48) or oral cephalexin 250 mg qid (N = 38), for 14 days. Six patients in the cefixime group and no patients in cephalexin group experienced diarrhea (p = 0.013). While the diarrhea was mild in all instances,

1 patient requested to be removed from the study for this symptom. Five patients in the cephalexin group and 3 patients in the cefixime group experienced nausea.

To compare the efficacy of cefixime and amoxicillin for lower or upper respiratory tract infections (LRTI or URTI), Kiani et al. (Kiani, 1988) performed 2 randomized, double-blind, 2-treatment, multi-centre studies, 1 for LRTI and another for URTI. Patients were randomly assigned to receive oral cefixime 400 mg qd (N = 282) or oral amoxicillin 500 mg t.i.d (N = 122) or 250 mg t.i.d (N = 156), for 10 -14 days. The AEs reported during both studies were similar in nature and frequency to those reported for other beta-lactam antibiotics with the exception of a higher incidence of altered bowel movement (diarrhea and stool changes) with both drugs. These episodes usually resolved without remedial medication when the treatment was withdrawn. No significant adverse laboratory findings were observed. The authors concluded that cefixime at a dosage of 400 mg once daily is an effective and safe oral antibiotic for the treatment of acute RTI.

### **Uncomplicated Gonorrhea**

In a randomized open-label study, 351 male patients with uncomplicated gonorrhea were given single oral doses of cefixime 400 mg (N = 150) or grepafloxacin 400 mg (N = 149) (Hook, 1997). Only 8 AEs were reported among the 351 study participants. The most common AEs in grepafloxacin-treated patients were nausea (4%), headache (3%), and pruritus (2%), while patients receiving cefixime most commonly reported headache (3%) and nausea (2%). Two grepafloxacin-treated patients reported potentially serious AEs. One developed severe nausea but recovered without treatment for the event. The second patient developed severe balanitis of unknown etiology and was withdrawn from the study. No clinically significant changes were detected in any patient by laboratory tests.

Miller et al. (Miller, 1997) conducted a retrospective review of clinic records over a 3-year period of patients treated with a single 400 mg dose of cefixime (N = 102) for gonorrhea during pregnancy. Cefixime was well tolerated; only 2 patients, both of whom also received azithromycin, experienced nausea and vomiting. A third patient receiving no other antibiotics had diarrhea. No patient reported a skin rash or respiratory difficulty. Delivery information was sought from review of records and follow-up contact with patients, when available. One patient aborted 3 weeks after treatment at 18 weeks gestation. Delivery at < 37 weeks occurred in 10 of 74 patients. Birth weight was < 2,500 g in 15 of 74 patients; only 1 of these was < 1,500 g. Both low birth weight (20.2%) and preterm delivery (13.5%) are consistent with the patient population served. The authors concluded that a single 400 mg oral dose of cefixime was effective for the treatment of gonorrhea and was well tolerated by the pregnant women.

A randomized study was conducted to compare the clinical efficacy and tolerability of a single 800 mg oral dose of cefixime with those of an established regimen, namely amoxicillin and probenecid, in the treatment of uncomplicated gonorrhea in men (Megran, 1990). Patients were randomized in a 2:1 ratio to receive a single oral dose of either cefixime 800 mg (N = 99) or amoxicillin 3.0 g and probenecid 1.0 g (N = 47). AEs were common with both treatment regimens and occurred in 31% and 30% of cefixime- and amoxicillin-treated men, respectively. All AEs were mild and resolved spontaneously. The most common complaints were lower

NDA 203195  
Suprax<sup>®</sup> 400 mg Capsules

gastrointestinal in nature and included diarrhea, loose stools, and cramping abdominal pain. The authors concluded that cefixime was well-tolerated, and all side effects were mild and self-limited.

### **Deaths**

No deaths were reported in the bioequivalence study conducted for Lupin's proposed cefixime capsules.

One death was reported in the published literature (Lorenz, 1998), in which a patient exposed to cefixime died during the study from an extended carcinoma of the gall bladder and sigma that was undiagnosed at study entry.

### **Other Serious Adverse Events**

No serious AEs were reported in the bioequivalence study conducted for Lupin's proposed cefixime capsules.

### **Other Significant Adverse Events**

One subject withdrew from the last dosing phase of the bioequivalence study LBC-10-044 because of an AE (fever). Fever was present on the morning on which the subject was to receive cefixime capsule 400 mg. The subject therefore was not dosed.

### ***Medical Officer's Comments:***

*The safety profile of cefixime is acceptable. The side effects are generally mild and self-limited.*

## 9.2 Labeling Recommendations

A PLR draft labeling has been submitted by the applicant that will be reviewed under separate cover. Of note, the review division requested that the applicant provide PLR labeling that included not only the 400-mg capsule formulation for this NDA, but also included the tablet and oral suspension formulations also marketed by Lupin Limited. Once approved with this NDA, the labeling for the generic cefixime products marketed by Lupin Limited will be changed to match the approved PLR labeling.

## 9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not scheduled for discussion of this NDA submission; it was not considered necessary for this application.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

NASIM R MOLEDINA  
05/09/2012

JOHN J ALEXANDER  
05/10/2012

# Clinical Review of NDA

**NDA:** 203,195

**Date of Submission:** June 28, 2011

**Date of Review:** October 26, 2011

**Applicant:** Lupin Pharmaceuticals

**Drug - Generic:** Cefixime

**Trade:** Suprax® (cefixime) Capsules

**Class:** Cephalosporin

**Related NDA:** 50-622

**Route of Administration:** Oral

## Purpose of Submission

The Sponsor has submitted this new drug application (NDA) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. A 505(b)(2) application may include results of investigations necessary for approval but were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [21 U.S.C. 355(b)(2)]. The application contains labeling which must be reviewed and approved prior to the approval of the application. During the review of the labeling, the Geriatric Use subsection under the **USE IN SPECIFIC POPULATIONS** section was found to be missing. The Sponsor was contacted regarding this deficiency and asked for an explanation. (b) (4)

(b) (4)  
No additional information was provided.

(b) (4)

## **Revised Geriatric Use subsection**

This subsection has been updated according to regulations found under 21 CFR 201.57(v)(B)(1), (C)(1) and (2). The revised statement reads as follows:

“Clinical studies of Suprax 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 pharmacokinetics study in the young and elderly detected differences in pharmacokinetic parameters (see CLINICAL PHARMACOLOGY). However, the differences were small and do not indicate a need for dosage adjustment in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal (see DOSAGE AND ADMINISTRATION), or cardiac function, and of concomitant disease or other drug therapy.

“This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.”

#### RECOMMENDATION

It is recommended that the revised statement above be included in a new Geriatric Use subsection (8.5), under the Use in Specific Populations section.

---

James Blank, Ph.D.  
Clinical Reviewer, DAIOP

---

John Alexander, M.D., M.P.H.  
Medical Team Leader, DAIOP

Word/203,195 Draft-10-26-11

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JAMES G BLANK  
10/26/2011

JOHN J ALEXANDER  
10/26/2011



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not Applicable

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The Applicant did not include a pediatric assessment statement or a request for a deferral or waiver of pediatric studies. The Applicant should provide a pediatric assessment that addresses whether there is sufficient information to support pediatric use of cefixime for each of the indications in the labeling. The applicant should ask for a waiver or deferral of pediatric studies for all or some specific indications, if the information to support pediatric use is not adequate (e.g., pediatric patients less than 6 months of age).

James Blank, Ph.D.	September 12, 2011
Reviewing Medical Officer	Date
John Alexander, M.D., M.P.H.	September 12, 2011
Clinical Team Leader	Date

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JAMES G BLANK  
09/12/2011

JOHN J ALEXANDER  
09/12/2011