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APPLICATION NUMBER:

202091Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type 505(b)(2), Resubmission/Class 2
Application Number NDA 202091
Priority or Standard Standard

Submit Date 08/17/2012
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Division / Office DAIP/OND

Reviewer Name Dmitri Iarikov
Review Completion Date January 6, 2013

Established Name Cefixime oral suspension
(Proposed) Trade Name SUPRAX® (Cefixime for Oral
Suspension, 500 mg/5 mL)
Therapeutic Class Cephalosporin
Applicant Lupin Limited

Formulation Oral suspension
Dosing Regimen Weight based
Indications Uncomplicated urinary tract infections,
otitis media, pharyngitis
and tonsillitis, (b) (4)
acute exacerbations of chronic
bronchitis, uncomplicated gonorrhea
(cervical/urethral)

Intended Populations Adults and Children 6 months or older

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	5
1.1	Recommendation on Regulatory Action	5
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	5
1.4	Recommendations for Postmarket Requirements and Commitments	5
2	INTRODUCTION AND REGULATORY BACKGROUND	6
2.1	Product Information	6
2.4	Important Safety Issues With Consideration to Related Drugs.....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission	7
3	ETHICS AND GOOD CLINICAL PRACTICES.....	8
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	8
4.1	Chemistry Manufacturing and Controls	8
4.2	Clinical Microbiology.....	9
4.3	Preclinical Pharmacology/Toxicology	9
4.4	Clinical Pharmacology	9
4.4.1	Mechanism of Action.....	10
4.4.3	Pharmacokinetics.....	10
5	SOURCES OF CLINICAL DATA.....	11
5.2	Review Strategy	11
5.3	Discussion of Individual Studies/Clinical Trials.....	13
6	REVIEW OF EFFICACY	14
	Efficacy Summary.....	14
6.1	Indication	14
7	REVIEW OF SAFETY.....	14
	Safety Summary	14
8	POSTMARKET EXPERIENCE.....	15
9	APPENDICES	15
9.1	Literature Review/References	15
9.2	Labeling Recommendations	15
9.3	Advisory Committee Meeting.....	16

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

Table of Tables

Table 1. Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime under Fasted and Fed Conditions.....	10
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Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

Table of Figures

Figure 1. Structural formula for cefixime.....	6
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is a 505(b)(2) NDA, class 2 resubmission subsequent to a complete response letter issued by the Agency on August 26, 2011. The reasons for non-approval of the initial submission were related to potential dosing mistakes due to inadequate labeling (b) (4) rather than to safety and efficacy of the drug product. The safety and efficacy of SUPRAX[®] Cefixime for oral suspension 500 mg/5 mL were deemed sufficiently supported by two bioavailability/bioequivalence studies showing that the 500 mg/5 mL oral suspension was bioequivalent to the 200 mg/5 mL suspension in healthy adults.

The resubmission satisfactorily addresses deficiencies delineated in the complete response letter. As was suggested by the Agency in order to avoid dosing mistakes the Applicant has revised the concentration of the drug product in the drug labeling information to read as 500 mg/5 mL instead of 100 mg/mL so that the labeling and packaging of this new strength are visually different from the currently marketed concentrations. (b) (4)

As recommended by the Agency during the resubmission review, pharmacists will dispense an appropriate dosing device with each Suprax prescription. This approach addresses concerns related to the previously proposed (b) (4).

Based on the submitted responses and data from bioavailability/bioequivalence studies, 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 Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Cefixime is a cephalosporin antibacterial for oral administration. Antibacterial action of cefixime results from inhibition of cell-wall synthesis and the drug is stable in the presence of beta-lactamase enzymes. Structure for cefixime is depicted in Figure 1.

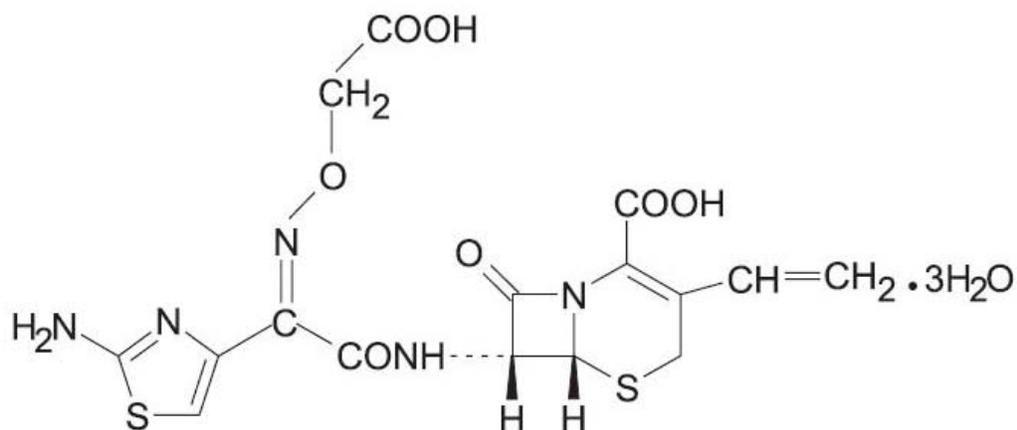


Figure 1. Structural formula for cefixime

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

Following cefixime formulations have been marketed in the US by the Applicant, Lupin pharmaceuticals:

- SUPRAX® Cefixime oral suspension 100mg/5 mL, ANDA 065129, approved 02/23/2004
- SUPRAX® Cefixime oral tablet 400 mg, ANDA 065130, approved 02/12/2004
- SUPRAX® Cefixime oral suspension 200 mg/5 mL, ANDA 065355, approved 04/10/2007
- SUPRAX® Cefixime chewable tablet, 100 mg, 150 mg, 200 mg, ANDA 065380, approved 10/25/2010
- SUPRAX® Cefixime oral capsule, 400 mg, NDA 203195, approved 06/01/2012

In addition, two cefixime products had been marketed in the US since 1989 and are currently discontinued but not for safety or efficacy reasons, SUPRAX® Cefixime oral tablet 200 mg and 400 mg, NDA 50-621, and SUPRAX® Cefixime oral suspension 100 mg/5 ml, NDA 50-622, both NDA were approved on April 28, 1989.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

2.4 Important Safety Issues With Consideration to Related Drugs

Cefixime oral suspension 500 mg/5 mL has a safety profile that is similar to other cephalosporins whose major safety issues include allergic reactions and the development of *Clostridium difficile* associated diarrhea.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial submission of NDA 202091 for Cefixime for oral suspension 100 mg/mL was received on October 27, 2010 and two amendments were submitted on December 13, 2010 and February 11, 2011, respectively.

The Applicant utilized the 505(b)(2) regulatory pathway citing Cefixime for oral suspension (ANDA 065355) 200 mg/5 mL as the reference listed drug (RLD). The submission relied upon two bioavailability studies showing that the 100 mg/mL oral suspension was bioequivalent to the 200 mg/5 mL suspension when both were given at a dose of 200 mg cefixime to healthy adults. For all background information and review of the initial application see review by Dr. James Blank from July 26, 2011.

The review of the initial application revealed several significant problems apparent:

1. (b) (4)
2. Serious medical errors due to similarities between the 100 mg/mL product and two other marketed concentrations of this oral suspension deemed possible.
3. (b) (4)

On January 3, 2011, the Division sent a letter to the Applicant asking them to provide

(b) (4)
The Division of Medication Error Prevention and Analysis (DMEPA) was consulted because of the concerns regarding potential for drug product confusion (mix-up) with three different concentrations of suspension available on the market and ability to deliver an accurate and reliable dose.

The complete response letter was issued on August 26, 2011 citing the following deficiencies and providing respective recommendations:

1. The introduction of the proposed suspension with overlapping numeric strength (100 mg/mL) to a suspension currently marketed (100 mg/5 mL) increases the potential for dosing errors. There may be underdosing (or overdosing) if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product, which poses safety and efficacy concerns. In order to resolve this deficiency, the following measures should be addressed:

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

- a. Revise the concentration to read 500 mg/5 mL. This will help to highlight the fact that the 100 mg/mL concentration is more concentrated than the currently marketed concentrations of 100 mg/5 mL or 200 mg/5 mL.
- b. Revise the container labels and carton labeling so that the labels, labeling, and packaging of this new strength will be visually different from the currently marketed concentrations.
- c. Conduct Human Factors testing to validate that differentiation of the strength and the use of other label enhancements are effective in minimizing the risk of confusion between the Suprax 100 mg/mL concentration and the currently marketed Suprax 100 mg/5 mL and 200 mg/5 mL concentrations.

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There were also additional comments on product quality which were not directly related to the clinical review and not provided here. On 08/20/2012 the applicant resubmitted the revised application.

3 Ethics and Good Clinical Practices

This NDA has been submitted as a 505(b)(2) application and included only two bioequivalence/bioavailability studies which did not raise any ethical concerns.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please, see the chemistry manufacturing and controls (CMC) review by Dr. Andrew Yu, PhD.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4)

Cefixime oral suspension 100 mg/mL

4.2 Clinical Microbiology

Cefixime has been shown to be active against most isolates of the following bacteria both in vitro and in clinical infections: *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Proteus mirabilis*, and *Neisseria gonorrhoeae*.

Suprax exhibits in vitro MICs of 1 mcg/mL or less against most ($\geq 90\%$) isolates of the following bacteria in vitro but the safety and effectiveness of Suprax in treating clinical infections due to these bacteria have not been established: *Streptococcus agalactiae*, *Haemophilus parainfluenzae*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Pasteurella multocida*, *Providencia species*, *Salmonella species*, *Shigella species*, *Citrobacter amalonaticus*, *Citrobacter diversus*, and *Serratia marcescens*.

Please see the microbiology review by Mr. Kerry Snow, for additional details.

4.3 Preclinical Pharmacology/Toxicology

No pharmacology/toxicology studies were included in this submission. The pharmacology/toxicology review for this product was written by Dr. Amy Nostrandt, PhD. The applicant refers to information found in the labeling for the reference listed drug, Suprax[®], in accordance with regulations found under 21 CFR 314.51(a)(3).

4.4 Clinical Pharmacology

The clinical pharmacology review was written by Dr. Yongheng Zhou, PhD. Please, see this review as well as the clinical review written by Dr. James Blank, MD for more details. In summary, the Applicant conducted two bioequivalence studies demonstrating bioequivalence of SUPRAX[®] Cefixime for Oral Suspension 100 mg/mL to the RLD. Each trial enrolled 24 subjects.

- Trial 312-07: An 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 fasting conditions, and
- Trial 313-07: An 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.

In addition, the Applicant also submitted an in vitro dissolution study comparing the dissolution profiles between the test formulation and RLD. The clinical pharmacology information provided by the Applicant was found to be acceptable and it was concluded that the proposed formulation met the bioequivalence criteria.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

4.4.1 Mechanism of Action

Antibacterial action of cefixime results from inhibition of cell-wall synthesis and the drug is stable in the presence of beta-lactamase enzymes.

4.4.3 Pharmacokinetics

The proposed formulation met the bioequivalence criteria with respect to the rate and extent of absorption (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) of cefixime under both fed and fasted conditions, Table 1.

Table 1. Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime under Fasted and Fed Conditions.

Fasted:

Parameters (Units)	In-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_{max} ($\mu\text{g/mL}$)	3.636	3.283	110.8	104.23 – 117.71%
AUC_{0-t} ($\mu\text{g}\cdot\text{h/mL}$)	29.736	26.702	111.4	103.97 – 119.29%
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	30.210	27.284	110.7	103.59 – 118.36%

Source: Study 312-07 Final Report

Fed:

Parameters (Units)	(In-transformed) 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_{max} ($\mu\text{g/mL}$)	1.773	1.892	93.7
AUC_{0-t} ($\mu\text{g}\cdot\text{h/mL}$)	14.531	15.375	94.5	85.58 - 104.38%
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	15.088	15.897	94.9	86.22 - 104.48%

Source: Study 313-07 Final Report

The proposed dose schedule for Lupin's cefixime 500 mg/5 mL oral suspension for adults and children is the same as for other cefixime suspension formulations and is as follows:

- Adults: 400 mg daily (400 mg qd or 200 mg bid). For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.
- Children: 8 mg/kg/day. This may be administered as a single daily dose or may be given in 2 divided doses, as 4 mg/kg every 12 hours. Children weighing more than (b) (4) or older than 12 years should be treated with the recommended adult dose.

5 Sources of Clinical Data

The Applicant is relying on (1) two bioavailability/bioequivalence studies conducted by Lupin, (2) previous finding of safety and efficacy for the reference listed drug (RLD) SUPRAX® Cefixime for oral suspension 200 mg/5 mL, ANDA 065355, and (3) safety and efficacy data from the published literature for cefixime. No new clinical trials demonstrating safety and efficacy of SUPRAX® Cefixime for Oral Suspension 500 mg/5 mL are included in the resubmission.

5.2 Review Strategy

The reviewer will assess the Applicant's responses to the deficiencies listed in the complete response letter that the Applicant provided in the resubmission. Safety update report analysis is included in Section 7, Review of Safety.

The following deficiencies relevant to the clinical review were listed in the complete response letter.

1. The introduction of the proposed suspension with overlapping numeric strength (100 mg/mL) to a suspension currently marketed (100 mg/5 mL) increases the potential for dosing errors. There may be underdosing (or overdosing) if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product, which poses safety and efficacy concerns. In order to resolve this deficiency, the following measures should be addressed:
 - a. Revise the concentration to read 500 mg/5 mL. This will help to highlight the fact that the 100 mg/mL concentration is more concentrated than the currently marketed concentrations of 100 mg/5 mL or 200 mg/5 mL.
 - b. Revise the container labels and carton labeling so that the labels, labeling, and packaging of this new strength will be visually different from the currently marketed concentrations.

Medical Officer's (MO) comments: The Applicant has revised the concentration of the drug product to read 500 mg/5 mL in the container labels, carton labeling and insert labeling so that the labels, labeling, and packaging of this new strength are visually different from the currently marketed concentrations.

- c. Conduct Human Factors testing to validate that differentiation of the strength and the use of other label enhancements are effective in minimizing the risk of confusion between the Suprax 100 mg/mL concentration and the currently marketed Suprax 100 mg/5 mL and 200 mg/5 mL concentrations.

MO comments: The Applicant conducted a study involving pharmacists and pharmacy technicians in retail and hospital pharmacies with the goal to determine whether they could choose the correct concentration of the drug (based on a simulated prescription or hospital order) and correctly fill a prescription for Suprax suspension from the three alternative concentrations.

(b) (4)

The study comprised the following cohorts: retail pharmacists (15), retail pharmacy technicians (15), hospital pharmacists (15), hospital pharmacy technicians (15), nurse caregivers (15), and parents (15).

The study demonstrated that participants were able to correctly dispense and dose the drug product. None of the pharmacists made an error in selecting the correct concentration from the mock shelf, and 93% of the technicians selected correctly (28 of the 30 subjects).

(b) (4)

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(b) (4)

4.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

satisfactorily addressed deficiencies 1 and 2 above, you may wish to consider limiting the use of the 100 mg/mL suspension to children above a specified minimum body weight or age.

MO comments: In response to the Agency recommendations the Applicant proposed a redesigned (b) (4)

(b) (4)

(b) (4)

(b) (4)

5.3 Discussion of Individual Studies/Clinical Trials

Please, see the discussion of the results of a Human Factors study conducted since the issuance of the complete response letter in section 5.2 Review Strategy. No other additional studies have been conducted since the submission of the initial NDA on October 27, 2010.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

6 Review of Efficacy

Efficacy Summary

SUPRAX® Cefixime for oral suspension 500mg/5 mL was demonstrated to be bioequivalent to the reference listed drug SUPRAX® Cefixime for oral suspension 200 mg/5 mL, ANDA 065355. The applicant is relying on the previous finding of efficacy for cefixime products.

6.1 Indication

- Uncomplicated urinary tract infections
- Otitis media
- Pharyngitis and tonsillitis
- (b) (4) acute exacerbations of chronic bronchitis
- Uncomplicated gonorrhea (cervical/urethral)

7 Review of Safety

Safety Summary

The applicant is relying on the previous finding of safety for the RLD. In addition, the initial NDA submission also included a list of 18 literature references related to cefixime as well as a computerized search of FDA's Adverse Event Reporting System Database (AERS) for outcomes of death and life-threatening conditions for period from March 17, 2006 to March 17, 2011. These materials were reviewed by Dr. Blank. No unexpected safety findings have been demonstrated.

In the resubmission in August 2012 the Applicant provided a safety update report. The report indicates that since submission of NDA 202,091 for cefixime suspension, 100 mg/mL on October 25, 2010 Lupin has not released any product for distribution nor conducted any additional nonclinical or clinical studies with the product. Therefore, no new safety data has been generated for SUPRAX (Cefixime) Oral Suspension, 100 mg/mL.

A search of the Entrez PubMed database was conducted with the term "cefixime" or "Suprax" for the period from October 26, 2010 to October 20, 2011 regarding the safety of the active ingredient cefixime. A search of the FDA's Adverse Events Reporting System (AERS) database on all data available from the fourth quarter of 2010 through the first quarter of 2011 was also conducted.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

The Entrez PubMed search identified 2 case reports. One report describing cefixime-induced nonconvulsive status epilepticus (NCSE) [1], and another described cefixime-induced hepatotoxicity [2].

In addition, the FDA's AERS database was reviewed for reports of adverse events (AEs) worldwide involving cefixime. The database was searched for "cefixime" or "Suprax". At the time of the search, 20 October 2011, data within the reporting period were available for the fourth quarters of 2010 and the first quarter of 2011, including October 2010 through March 2011.

The adverse events reported for AERS search were consistent with adverse events associated with the use of cephalosporins.

MO comments: No unexpected safety finding for cefixime have been identified by the safety updates. Seizures, including NCSE, are a known adverse reaction associated with cephalosporins and an adverse event of seizures is included in the cefixime labeling.

The case report of hepatotoxicity describes a transient elevation of transaminase that coincided with administration of cefixime overall consistent with grade 2 toxicity as per National Cancer Institute Toxicity Criteria. Elevations in liver functions test have been included in the Adverse Reactions section of cefixime label and do not represent an unexpected finding.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

1. Anzellotti F et al. Cefixime-induced nonconvulsive status epilepticus. *Neurol Sci.* 2012 Apr; 33(2):325-9.
2. Yilmaz B, Ekiz F et al. Cefixime-induced hepatotoxicity. *Turk J Gastroenterol.* 2011 Aug; 22(4):445.

9.2 Labeling Recommendations

A draft labeling has been submitted and will be reviewed separately.

Clinical Review

Reviewer: Dmitri Iarikov, MD, PhD.

NDA 202091

(b) (4) Cefixime oral suspension 100 mg/mL

9.3 Advisory Committee Meeting

No advisory committee was deemed necessary for this NDA resubmission.

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/s/

DMITRI IARIKOV
01/09/2013

JOHN J ALEXANDER
01/09/2013

Deputy Division Director's Decisional Memo

Date	August 26, 2011
From	Katherine Laessig, M.D.
Subject	Deputy Division Director's Decisional Memo
NDA #	202-091
Applicant Name	Lupin Pharmaceuticals, Inc.
Date of Submission	10/25/2010
PDUFA Goal Date	8/27/2011
Proprietary Name / Established (USAN) Name	SUPRAX® (cefixime)
Dosage Forms / Strength	Cefixime for oral suspension, 100 mg/mL
Proposed Indication	For the treatment of uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; ^{(b) (4)} acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral)
Action:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
Clinical Review	James Blank, Ph.D.
Cross Discipline Team Leader Memo	Kimberly Bergman, Pharm.D.
Clinical Pharmacology Review	Yongheng Zhang, Ph.D.
ONDQA Review	Andrew Yu, Ph.D.
ONDQA Biopharmaceutics Review	Mark Seggel, Ph.D.
DMEPA Review	Denise Baugh, Pharm.D., BCPS

1.0 Background

The applicant has submitted this NDA in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to support a new strength for an oral suspension of cefixime of 100 mg/mL. This NDA relies on the Agency's prior determination of safety and effectiveness for the reference listed drug (RLD), SUPRAX. The application also contains the results of two bioavailability (BA)/bioequivalence (BE) studies to establish a bridge to the RLD SUPRAX Cefixime for Oral Suspension, USP, 200 mg/5 mL (ANDA #A065355). These studies are Phase 1, open-label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral BE studies under fasted and fed conditions, respectively. A second cefixime for oral suspension is approved at a

concentration of 100 mg/5 mL. At this time, the applicant has stated they have no definite plan to discontinue either of the two currently approved oral suspensions.

Cefixime is a member of the cephalosporin class of antibacterial drugs that acts by inhibiting bacterial cell wall synthesis. It has been marketed in the U.S. for many years, initially by Lederle Laboratories. The original applications for Suprax oral tablets and oral suspension were both approved on April 28, 1989.

This memo will summarize the reviews by discipline for this study report. For more information, please refer to the reviews of each respective discipline, as well as the Cross Discipline Team Leader memo. Please note that there was no new pharmacology/toxicology, clinical microbiology, or clinical efficacy data contained in this supplement.

2.0 Chemistry, Manufacturing, and Controls

The ONDQA reviewer, Dr. Andrew Yu, does not recommend approval of this NDA because (b) (4)

In addition, there are a number of outstanding information requests that need to be addressed by the applicant. Significant findings from his review are discussed below.

The drug substance, cefixime USP, manufactured by Lupin Pharmaceuticals, Inc. is referenced by DMF 15996. Lupin is also the DMF holder and the DMF is current and adequate. Cefixime for oral suspension 100 mg/mL is an off-white to cream colored powder forming an off-white to pale yellow suspension with a characteristic fruity odor after reconstitution. Each mL of reconstituted suspension contains 100 mg of cefixime as trihydrate. Prior to reconstitution, the drug product should be stored at 20-25°C (b) (4). After reconstitution, the suspension may be kept for 14 days either at room temperature, or under refrigeration without significant loss of potency.

(b) (4)

specifications and fill weights/volumes will be communicated in the complete response letter. The shelf life of 24 months at USP controlled temperature is based on stability data for three stability batches at 21-24 months and additional stability data under accelerated conditions. These data are adequate to support the proposed 24 month shelf life.

2.0 Summary of Clinical Pharmacology

As noted above, this NDA contained clinical data from two BA/BE studies conducted by the applicant as follows:

- Study 312-07: 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 PK profile of cefixime 100 mg/mL oral suspension with respect to cefixime 200 mg/5 mL in healthy adult subjects under fasting conditions and to assess the bioequivalence, and
- Study 313-07: 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 PK profile of cefixime 100 mg/mL oral suspension with respect to cefixime 200 mg/5 mL in healthy adult subjects under fed conditions and to assess the bioequivalence.

The results of the two studies demonstrated that the 90% confidence intervals for the geometric mean test-to-reference for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were within the FDA bioequivalence acceptance range of 80 to 125% under both fed and fasted conditions. Dr. Zhang finds that the clinical pharmacology information contained in this application is acceptable.

3.0 Summary of Safety

The applicant provided a review of the literature that did not identify any new safety signals. In addition, a computerized search of AERS did not identify any new safety signals either.

The clinical reviewer, Dr. James Blank, notes that there are potential safety issues for dosing and medication errors, given that there are already two marketed cefixime oral suspension formulations of differing concentrations, and approval of this application would provide for a third. The applicant had initially proposed a (b) (4). The proposed (b) (4) proposed in the product labeling (b) (4) who may spit out the dose may result in under dosing, which may result in treatment failure or select for resistant bacteria. In contrast, should the incorrect suspension be dispensed, a patient may be at risk of receiving a dose up to five fold the recommended dose, posing the possibility of

increased adverse reactions. Therefore, the clinical reviewer does not recommend approval of this application due to the potential for medication and dosing errors.

4.0 Summary of DMEPA Review

The Division of Medication Error Prevention and Analysis provided a review of the potential for medication errors for this application. They determined that the introduction of this new suspension with overlapping numeric strength to the currently marketed suspensions increases the potential for dosing errors, and increases the potential for underdosing or overdosing if the 100 mg/mL suspension is confused with the 100 mg/5 mL suspension, the risks of which are noted above. (b) (4)

The DMEPA reviewer recommends specific measures to reduce the risks of drug errors prior to approval.

5.0 Recommended Regulatory Action

I concur with the recommendations of the review team that the potential for dosing and medication errors with this proposed (b) (4) and (b) (4), with consequent risks for increased adverse events, treatment failure, and development of resistance. Therefore, I do not recommend approval of the application in its current form. The applicant will be issued a Complete Response letter outlining the deficiencies, and the means to address them as described below. In addition, the CMC information requests that are not deficiencies will be included in the letter as well.

1. The introduction of the proposed suspension with overlapping numeric strength (100 mg/mL) to a suspension currently marketed (100 mg/5 mL) increases the potential for dosing errors. There may be underdosing (or overdosing) if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product, which poses safety and efficacy concerns. In order to resolve this deficiency, the following measures should be addressed:
 - a. Revise the concentration to read 500 mg/5 mL. This will help to highlight the fact that the 100 mg/mL concentration is more concentrated than the currently marketed concentrations of 100 mg/5 mL or 200 mg/5 mL.

- b. Revise the container labels and carton labeling so that the labels, labeling, and packaging of this new strength will be visually different from the currently marketed concentrations.
- c. Conduct Human Factors testing to validate that differentiation of the strength and the use of other label enhancements are effective in minimizing the risk of confusion between the SUPRAX 100 mg/mL concentration and the currently marketed SUPRAX 100 mg/5 mL and 200 mg/5 mL concentrations.



(b) (4)



(b) (4)

PRODUCT QUALITY

The following are requests for information that also need to be addressed:

1. Provide target fill weight with ranges for the powder fill of each configuration of your product.
2. Indicate how the average fill weights are determined (how many units used for determination, frequency of sampling, etc.).
3. Clarify if there is overfill in your product. If so, specify the amount for each configuration.
4. Provide the total volume of the suspension after reconstitution for each configuration of your product at the target maximum and minimum fill weights, respectively. Provide the fill volumes at the target, maximum and minimum fill weights.
5. Clarify the regulatory acceptance criterion (NMT ^(b)% or NMT ^(b)%) for moisture analysis by ^{(b)(4)} method for your product.
6. Provide more information on the potential reactivity of sodium benzoate with components in the product.
7. The following changes to the drug product specifications are recommended:
 - i.* A single acceptance criterion for drug product release and stability.
 - ii.* Based on the review of your stability data, the acceptance criterion for total impurity should be tightened from NMT ^{(b)(4)}% to NMT ^{(b)(4)}%. The acceptance criterion for the cefixime assay should be revised from ^{(b)(4)}% to ^{(b)(4)}%.
 - iii.* The upper limit of ^{(b)(4)}% in the USP is not currently justified based on manufacturing and stability considerations provided for this product.
 - iv.* The acceptance criterion for sodium benzoate should be revised from NLT ^{(b)(4)} mg/mL to NLT ^{(b)(4)} mg/mL based on data from your stability batches.
 - v.* Provide an updated specification for the drug product in the NDA reflecting all revisions.

Katherine A. Laessig, MD

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/s/

KATHERINE A LAESSIG
08/26/2011

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	August 9, 2011
From	Kimberly L. Bergman, Pharm.D.
Subject	Cross Discipline Team Leader Review
NDA #	202-091
Applicant	Lupin Pharmaceuticals, Inc.
Date of Submission	October 25, 2010
PDUFA Goal Date	August 26, 2011
Proprietary Name / Established (USAN) names	SUPRAX® (Cefixime)
Dosage forms / Strength	Cefixime for oral suspension, 100 mg/mL
Proposed Indication(s)	For the treatment of uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; (b)(4) acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral)
Recommended:	Complete Response

1. Introduction

Lupin Pharmaceuticals, Inc. submitted the 505(b)(2) application for Suprax® Cefixime for Oral Suspension, (b)(4). The reference listed drug (RLD) to support the safety and efficacy of the product is Suprax® Cefixime for Oral Suspension USP, 200 mg/5mL, approved in 2007 under ANDA #A065355 from the same applicant. Cefixime has been previously approved for oral administration in four tablet strengths (100, 150, 200 and 400 mg) and two suspension concentrations (200 mg/5mL and 100 mg/5 mL). The proposed cefixime (b)(4) product has been developed to offer a new treatment option for children, and also adults who have difficulty swallowing oral tablets, as the proposed formulation is more concentrated than the currently available suspension formulations.

In support of the NDA, the Applicant conducted two bioequivalence (BE) studies (#312-07 and #313-07) to bridge the proposed formulation with the RLD. These two studies are Phase 1, open label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral BE studies under fasted and fed conditions, respectively.

This CDTL review summarizes the findings of the various discipline reviews.

2. Background

Cefixime is a semi-synthetic, cephalosporin antibiotic for oral administration and is an active ingredient in previously FDA-approved products with extensive marketing history. As with other cephalosporins, bactericidal action of cefixime results from inhibition of cell-wall synthesis. Cefixime is highly stable in the presence of beta-lactamase enzymes. Cefixime products are indicated in the treatment of the following infections when caused by susceptible strains of designated microorganisms: uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; (b)(4) acute exacerbations of chronic bronchitis; and uncomplicated gonorrhea (cervical/urethral).

Cefixime has been marketed in the U.S. for many years, initially by Lederle Laboratories. The original NDAs for Suprax® (oral tablet) (NDA 50-621) and Suprax® (cefixime for oral suspension) (NDA 50-622) were both approved on April 28, 1989. The NDA for SUPRAX® Cefixime for Oral Suspension, USP, 200 mg/5 mL (NDA 65-355) was approved on April 10, 2007. Cefixime is currently manufactured by Lupin Limited worldwide. Lupin Limited has marketed SUPRAX® since the approval of SUPRAX® Cefixime Tablets USP, 400 mg on February 12, 2004 (ANDA# A065130). Subsequently, Lupin received approval for SUPRAX®

Cross Discipline Team Leader Review

Cefixime for Oral Suspension USP, 100 mg/5 mL, (approved on February 23, 2004; ANDA# A065129), and SUPRAX® Cefixime for Oral Suspension USP, 200 mg/5 mL (approved on April 10, 2007; ANDA# A065355). Lupin is utilizing the 505(b)(2) pathway for the SUPRAX® Cefixime for Oral Suspension, 100 mg/5 mL because the proposed formulation of cefixime is a new strength for a previously approved product and the applicant is relying on (1) two bioavailability/bioequivalence studies conducted by Lupin, (2) FDA's previous findings of safety and efficacy for the RLD (Suprax), and (3) safety and efficacy data from the published literature for cefixime. The RLD to support the safety and efficacy of the proposed product is SUPRAX® Cefixime for Oral Suspension USP, 200 mg/5 mL.

The proposed dose schedule for Lupin's cefixime 100 mg/mL oral suspension for adults and children is the same as Suprax and is as follows:

- Adults: 400 mg daily (400 mg qd or 200 mg bid). For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.
- Children: 8 mg/kg/day. This may be administered as a single daily dose or may be given in 2 divided doses, as 4 mg/kg every 12 hours. Children weighing more than (b) (4) kg or older than 12 years should be treated with the recommended adult dose.

The proposed pediatric dose schedule for Lupin's cefixime 100 mg/mL oral suspension (b) (4)

Table 2.1 Proposed Pediatric Dosing Schedule for Cefixime Oral Suspension 100 mg/mL

A large rectangular area of the document is redacted with a solid grey box. The redaction covers the entire content of Table 2.1. A small label '(b) (4)' is visible in the top right corner of the redacted area.

In addition to a summary of data from the Summary Basis of Approval (SBA) for Suprax tablets and powder for oral suspension (FDA, 1988), published literature, and approved Suprax labeling (Lupin Pharma, 2008), this NDA presents clinical data from two bioavailability/bioequivalence (BA/BE) studies conducted by the applicant, as follows:

- **Study 312-07:** 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 fasting conditions and to assess the bioequivalence, and
- **Study 313-07:** 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.

3. CMC/Device

Drug Substance

The drug substance cefixime USP manufactured by Lupin Pharmaceuticals Inc. is supported by DMF 15996 (currently held by the applicant). The DMF is current and adequate.

Drug Product

The drug product Cefixime For Oral suspension contains 100 mg/mL of drug after reconstitution. The applicant's lower strengths of Cefixime For Oral suspension, 200 mg/5mL and 100mg/5mL are currently approved as ANDAs. (b) (4)



Manufacturing and Stability

The manufacturing of the powder For Oral suspension involves dry blending the active and inert excipients followed by milling to proper mesh sizes and the filled into bottles of different configurations. Appropriate in process controls are included to control blend uniformity, moisture, and other process parameters. CMC issues with stability, preservative, dissolution and product quality have been adequately responded to by the applicant except for the delivery syringe issue. Based on the stability data provided, some acceptance criteria in the drug product specification need to be tightened for improved quality. CMC information requests related to the specifications and fill weights/volumes were not communicated to the applicant in this review cycle due to the non-approvability of this NDA. The requests will be included in the Complete Response letter (see Section 13). The shelf life of 24 months at USP controlled room temperature is based on stability data for three stability batches at 21-24 months and additional stability data under accelerated conditions. The stability data provided are adequate to support the shelf life proposed.

Quality Assessment

The dissolution test proposed in the application is identical to the tests approved for the lower concentration products, except that for the 200 mg/5 mL product a sample containing the equivalent of 200 mg cefixime is introduced into each vessel while for the 100 mg/mL and 100 mg/5 mL suspensions the equivalent of only 100 mg cefixime is transferred to each vessel. USP Apparatus Type 2 is used at 50 rpm; the medium consists of 900-mL 0.05M potassium phosphate buffer of pH 7.2. The proposed acceptance criterion for the new product was NLT (b) (4) % (Q) dissolved after 30 minutes while the acceptance criterion for the approved products is NLT (b) (4) % (Q) at 30 minutes. At the (b) (4)'s request and for consistency, the applicant revised the acceptance criterion to NLT (b) (4) % (Q) at 30 minutes. The current USP monograph for Cefixime for Oral Suspension does not include a dissolution test. It should be noted that under the established test conditions, all cefixime suspensions are rapidly dissolved (greater than (b) (4) % in the first 10 minutes; dissolution is complete within 30 minutes). The established test therefore appears to have limited value as a quality control tool.

In summary, from a CMC perspective, NDA 202-091 is not recommended for approval as the (b) (4) the 100mg/ml cefixime formulation is inadequate to assure accurate delivery of doses to the pediatric populations provided for in the NDA. As CDTL reviewer, I agree with this recommendation, and this assessment is consistent with the Clinical Reviewer's and Division of Medication Error Prevention and Analysis (DMEPA) findings (see Section 8). Refer to the CMC reviews by Drs. Seggel (dated June 8, 2011) and Yu (dated June 27, 2011) for further information.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review focused on data from reproductive/developmental studies and its presentation in the proposed labeling. Proposed labeling is consistent with that of the RLD, however dose multiples for extrapolation from reproductive/developmental studies performed in rats and mice do not appear to be based on doses normalized for total body surface area (TBSA). According to the summary basis of approval for NDA 50-621, the highest dose used in segment II studies in mice and rats was 3200 mg/kg/day. That dose was stated to be not embryotoxic or teratogenic in both species. The NOAEL dose for effects on fertility was stated in the FDA review to be 1000 mg/kg/day in rats. The dose multiples in the proposed label appear to have been derived by dividing these nominal doses by a human dose of 8 mg/kg/day, arriving at dose multiples of 400 for developmental and reproductive toxicity studies and 125 for the fertility study.

The Nonclinical reviewer recommends that dose multiples for extrapolation from nonclinical studies to clinical doses should be updated to the current standard; i.e. based on doses normalized for TBSA. The NOAEL in segment II studies in mice and rats would be equivalent to human doses (HED) of 267 mg/kg and 533 mg/kg, respectively. For a 60 kg patient, the lower of those would be approximately 16,000 mg/day or 40 times the adult dose, not 400 times the dose as currently stated in the label. Similarly, the NOAEL dose for effects on fertility in rats would be equivalent to a human dose of 167 mg/kg/day, or 10,000 mg/day for a 60 kg patient).

(b) (4)

In summary, it is recommended that the proposed label, as well as the referenced label(s), be updated and the description of the nonclinical reproductive and developmental toxicity data be revised. As CDTL reviewer, I agree with this recommendation. This recommendation should be addressed in a future review cycle, as labeling will not reviewed during the current cycle due to issuance of a Complete Response. Refer to the Nonclinical Pharmacology/Toxicology Memo to File by Dr. Nostrandt dated April 21, 2011 for further information.

5. Clinical Pharmacology

In support of this 505(b)(2) application, the Applicant conducted two BE studies (#312-07 & #313-07) to bridge the proposed formulation with the RLD. These two studies are Phase 1, open label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral BE studies under fasted and fed conditions, respectively. The primary variable for comparison in these studies was the pharmacokinetics of cefixime following administration of the proposed and RLD formulations, specifically C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$. Statistical comparisons of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ for the two formulations are summarized in Tables 5.1 and 5.2. The proposed formulation met the bioequivalence criteria with respect to the rate and extent of absorption (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) of cefixime under both fed and fasted conditions. The Clinical Pharmacology information provided by the applicant in the NDA submission was deemed acceptable by the Clinical Pharmacology Reviewer. As CDTL reviewer, I concur with this assessment. Refer to the Clinical Pharmacology review by Dr. Zhang dated June 1, 2011 for further information.

Table 5.1 Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Comparison of Cefixime Exposure - Fasted

Parameters (Units)	ln-transformed data			
	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: 100 mg/mL (fasted)	A: 200 mg/5 mL (fasted)	Ratio (B / A)%	
C_{max} (µg/mL)	3.636	3.283	110.8	104.23 – 117.71%
AUC_{0-t} (µg*h/mL)	29.736	26.702	111.4	103.97 – 119.29%
$AUC_{0-\infty}$ (µg*h/mL)	30.210	27.284	110.7	103.59 – 118.36%

Source: Study 312-07 Final Report

Table 5.2 Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Comparison of Cefixime Exposure - Fed

Parameters (Units)	(ln-transformed) 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 _{max} (µg/mL)	1.773	1.892	93.7	84.48 - 103.88%
AUC _{0-t} (µg*h/mL)	14.531	15.375	94.5	85.58 - 104.38%
AUC _{0-∞} (µg*h/mL)	15.088	15.897	94.9	86.22 - 104.48%

Source: Study 313-07 Final Report

6. Clinical Microbiology

No new clinical microbiology data were submitted with this application.

7. Clinical/Statistical- Efficacy

No new clinical efficacy data were submitted with this application. The applicant is relying on the previous findings of efficacy for the reference listed drug, SUPRAX®. The applicant included a review of published studies that contain both efficacy and safety data to support the application, as summarized in Table 7.1.

Table 7.1 Summary of Clinical Efficacy Studies for Cefixime from Published Literature

Indication	Study Designs	Formulation	Number of Cefixime-Treated Patients	Dose Range	Efficacy Conclusions
Urinary Tract Infections (UTI)	Randomized, prospective; Phase 4, open-label, nonrandomized; Placebo-controlled, prospective, randomized, double-blind trials	Oral Tablets or Capsules or Suspension	244: children and adults; both males and females	8 mg/kg/day or 200 mg bid or 400 mg qd or 400 mg single dose	Clinical cure: 77.3% - 92% Bacteriological cure: 63.6% - 83%
Acute Otitis Media (AOM)	Randomized; Multicentre open-label, randomized trials	Oral Suspension	318: children < 10 y; both males and females	8 mg/kg/day: 8 mg/kg qd or 4 mg/kg bid	Clinical cure: 90% Bacteriological cure: 74% - 86.7%
Respiratory Tract Infections (RTI)	Double-blind randomized; Randomized open-label; Phase 4, open-label, nonrandomized trials	Oral Tablets or Suspension	960: children and adults; both males and females	8 mg/kg qd or 200 mg bid or 400 mg qd	Clinical cure: 49% - 100% Clinical cure or improvement: 90% - 100% Bacteriological cure: 54% - 100% Radiographic clearing or Improvement: 66% - 70%
Uncomplicated Gonorrhoea	Randomized trials; Retrospective review of clinic records	Oral Tablets or Capsules	351: ≥ 14 y; both males and females	400 mg single dose or 800 mg single dose	Clinical cure: 99% Bacteriological cure: 95.2% - 99%

Source: NDA 202-091, Section 2.7.3 Summary of Clinical Efficacy, Table 2.7.3-15

According to the applicant’s analysis and conclusions from this literature review, in conjunction with previous findings of efficacy for the reference listed drug:

Cross Discipline Team Leader Review

- Six clinical studies (244 patients receiving cefixime) from published literature showed that cefixime is effective in treating UTI;
- One clinical study mentioned in the Suprax label (221 patients receiving cefixime) and two clinical studies (318 patients receiving cefixime) from the published literature showed that cefixime is effective in treating AOM;
- One clinical study discussed in the SBA (401 patients receiving cefixime) and seven clinical studies (960 patients receiving cefixime) from published literature showed that cefixime is effective in treating RTI; and
- Three clinical studies (351 patients receiving cefixime) from published literature showed that cefixime is effective in treating uncomplicated gonorrhea.

Based on the Clinical Reviewer's assessment of the submitted literature reports, the information presented in the current submission is consistent with the previous findings of efficacy demonstrated for the RLD, SUPRAX®. As CDTL reviewer, I concur with this assessment. Refer to the Clinical review by Dr. Blank dated July 26, 2011 for further information.

8. Safety

Clinical Safety Review

The applicant is relying on the previous finding of safety for the RLD, SUPRAX®, with supportive data from the aforementioned literature reports. The Clinical Safety review focused on current AERS information and an assessment of the potential for medication errors with the proposed drug product.

1. AERS Database

A computerized search of FDA's AERS was conducted for the purpose of identifying any recent changes in the safety profile for cefixime. The search retrieved 5 reports, with 2 deaths and 3 life-threatening situations. All of the reports were foreign. The cases involving the 2 deaths were examined for more information and the reports are summarized as follows:

- A. ISR report #5892568: a 40 year-old woman from Bangladesh who underwent a total abdominal hysterectomy for chronic cervicitis. After surgery she received cefixime, ranitidine, ceftriaxone, azithromycin and diclofenic. Doses for each medication and duration of therapy were not listed in the ISR report. The patient developed Stevens-Johnson Syndrome and mild anemia after taking cefixime, along with the other medications.
- B. ISR report #6553714: a 63 year-old man from France who expired due to bone marrow failure after receiving 10 medications including Oroken (cefixime), total dose 400 mg. The primary suspect drug was listed as ciprofloxacin, while cefixime was considered a secondary suspect drug, along with Temodal and Solupred. Concomitant medications included: Mopral (omeprazole), Pyostacine, Vancomycine, Amiklin (amikacin sulfate), and Fortum (ceftazidime).

2. Medication Error Assessment

The applicant currently markets two concentrations of cefixime suspension; 100 mg/5 mL (20 mg/mL) and 200 mg/5 mL (40 mg/mL). The suspension proposed in this NDA is of higher concentration, containing 100 mg/mL of cefixime and is ^(b)₍₄₎ and ^(b)₍₄₎ times more concentrated than the currently marketed 200 mg/5 mL and 100 mg/5 mL suspensions, respectively. From the Clinical Reviewer's perspective, the availability of three different concentrations of cefixime suspension increases potential for medication dispensing error related to suspension strength.

(b) (4)

Based on the Clinical Reviewer's assessment of the safety concerns outlined above, NDA 202-091 should not be approved in its present form. The Clinical Reviewer's safety findings are consistent with the CMC and DMEPA reviews and as CDTL reviewer, I concur with the Clinical Reviewer's assessment of safety. Refer to the Clinical review by Dr. Blank dated July 26, 2011 for further information.

Division of Medication Error Prevention and Analysis (DMEPA) Review

This review evaluated the potential for medication errors with introduction of 1) the 100 mg/mL strength, and (b) (4) (Cefixime Oral Suspension) under this 505(b)(2) application.

1. Introduction of the 100 mg/mL Strength

The proposed Suprax Oral Suspension 100 mg/mL introduces a third concentration into the marketplace (i.e., 100 mg/mL, 100 mg/5 mL, and 200 mg/5 mL). This new concentration has a numeric overlap with and is (b) (4) times more concentrated than the currently marketed 100 mg/5 mL. Drug usage data demonstrates that Suprax is currently prescribed by concentration and a corresponding teaspoon or mL dose. However, despite the inclusion of a concentration on the prescription, errors within the Suprax product line may occur during the prescribing and dispensing of Suprax. The DMEPA reviewer has determined that the introduction of this new overlapping numeric strength increases the potential for dosing errors and for under or over dosing if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product. Examples of these errors include the following:

- The wrong concentration may be selected during prescribing in an electronic Computerized Prescriber Order Entry (CPOE) System and at the point of data entry into the pharmacy computer (100 mg/mL chosen instead of 100 mg/5 mL). Based on FDA post-marketing experience with other drug products having similar expressions of concentration, there is a heightened risk of confusion between the

Cross Discipline Team Leader Review

100 mg/mL and 100 mg/5 mL products. Because the dose of Suprax is most commonly expressed in volume (i.e. teaspoonfuls or X mL), these errors would go undetected and could result in an over or underdose depending on the strength selected as compared to the strength prescribed.

- Prescribers may order the “100 mg/mL” concentration but the pharmacist/pharmacy technician erroneously misinterprets the prescription as “100 mg/5 mL” to dispense to the patient (or vice versa) because they misread the prescription or selected the wrong concentration (on a computer screen or from the shelf).
- During prescribing, healthcare providers may confuse the 100 mg/mL and 100 mg/5 mL concentrations when calculating the doses and converting the dose in mg to the corresponding volume.

Of greatest concern are the errors related to confusion between the Suprax 100 mg/mL and 100 mg/5 mL concentrations which could result in 5-fold overdoses of Suprax. Such overdoses represent a significant safety concern as patients who receive this magnitude of overdose with Suprax are at risk for adverse events including nausea and vomiting resulting in dehydration, as well as increased potential for seizures. Since preliminary drug usage information indicates that most directions for the currently marketed Suprax products are written in a teaspoonful unit of measurement and Suprax 100 mg/5 mL is the concentration with which the medical community is most familiar, it is plausible that the five-fold overdose would occur if the 100 mg/mL concentration is allowed into the marketplace.

(b) (4)

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

No regulatory issues are outstanding for this application.

12. Labeling

Labeling will not be addressed during the current review cycle, due to the issuance of a Complete Response.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend the issuance of a Complete Response for this 505(b)(2) application.

- Risk Benefit Assessment

As the information presented in the current submission is consistent with the previous findings of efficacy for the reference listed drug, SUPRAX®, the risk-benefit assessment for this application focused on the following safety factors:

- The availability of three different concentrations of cefixime suspension (i.e., 100 mg/mL, 100 mg/5 mL, and 200 mg/5 mL), and specifically a new concentration that has a numeric overlap with and is ⁶ times more concentrated than the currently marketed 100 mg/5 mL concentration, increases potential for medication dispensing errors related to suspension strength. Overdoses represent a significant safety concern as patients who receive a 5-fold magnitude of overdose are at risk for adverse events including nausea and vomiting causing dehydration, as well as increased potential for seizures.

(b) (4)

Based on these factors, the risks for potential medication errors outweigh the benefits of treatment with the 100 mg/mL strength of cefixime oral suspension.

- Recommendation for Post-marketing Risk Management Activities

Not applicable.

- Recommendation for other Postmarketing Study Commitments

Not applicable.

- Recommended Comments to Applicant

The following deficiencies and comments will be conveyed to the applicant in the Complete Response letter:

CLINICAL

1. Two concentrations of cefixime suspension; 100 mg/5mL (20 mg/mL) and 200 mg/5 mL (40 mg/mL) are currently marketed. The suspension proposed in your application is of higher concentration, containing 100 mg/mL of cefixime and is (b) (4) and (b) (4) times more concentrated than the currently marketed 200 mg/5 mL and 100 mg/5 mL suspensions, respectively. The availability of three different concentrations of cefixime suspension increases potential for medication dispensing error related to suspension strength. Additional details regarding this deficiency and recommendations to address it are included below, as provided by the Division of Medication Error Prevention and Analysis (DMEPA).

2.



DMEPA

3. We have determined that the introduction of the proposed overlapping numeric strength (100 mg/mL) increases the potential for dosing errors with Suprax and increases the potential for under dosing (or over dosing) if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product. In order to address this deficiency, consider the following:

- a. Revise the concentration to read 500 mg/5 mL. This will help to highlight the fact that the 100 mg/mL concentration is more concentrated than the currently marketed concentrations of 100 mg/5 mL or 200 mg/5 mL.
- b. Revise the container labels and carton labeling so that the labels, labeling, and packaging of this new strength are visually different than the currently marketed concentrations.
- c. Conduct Human Factors testing to validate that differentiating the strength and the use of other label enhancements is effective in minimizing the risk of confusion between the Suprax 100 mg/mL concentration and the currently marketed Suprax 100 mg/5 mL and 200 mg/5 mL concentrations.



PRODUCT QUALITY

6. Please also provide a response to the following non-deficiency information requests (IR).
- a. Provide target fill weight with ranges for the powder fill of each configuration of your product. Also indicate how the average fill weights are determined (how many units used for determination, frequency of sampling, etc.).
 - b. Do you have overfill in your product? If so, how much for each configuration?
 - c. What is the total volume of the suspension after reconstitution for each configuration of your product at the target, maximum and minimum fill weights, respectively. Also, what are the fill volumes at the target, maximum and minimum fill weights?
 - d. Clarify the regulatory acceptance criteria for moisture analysis by (b) (4) method of your product (NMT (b) (4)% or NMT (b) (4)%?).
 - e. Provide more information on the potential reactivity of sodium benzoate with components in the product.
 - f. We recommend the following changes to your drug product specification:
 - i. A single acceptance criteria for drug product release and stability.
 - ii. Based on the review of your stability data, the acceptance criteria for total impurity be tightened from NMT (b) (4)% to NMT (b) (4)%. Acceptance criteria for the cefixime assay be revised from 90-120% to 90-110%.
 - iii. The upper limit of (b) (4) in the USP is not currently justified based on manufacturing and stability consideration from this product.
 - iv. We recommend the acceptance criteria for sodium benzoate be revised from NLT (b) (4) mg/mL to NLT (b) (4) mg/mL based on data of your stability batches.

Cross Discipline Team Leader Review

- v. Provide an updated specification for your drug product in the NDA reflecting all revisions.

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/s/

KIMBERLY L BERGMAN
08/11/2011

Clinical Review of Original NDA

NDA: 202,091

Supporting Document: 1

Sponsor: Lupin Pharmaceuticals, Inc.
Harborplace Tower
111 South Calvert Street, 21st Floor
Baltimore, MD 21202
Telephone: 410 576-2000
Fax: 410 576-2221

Date of Submission: October 25, 2010

Dates of Amendments: December 10, 2010
February 10, 2011

Date of Review: February 7, 2011

Drug - Generic: Cefixime

Trade: Suprax[®] (Cefixime for Oral Suspension, 100 mg/mL)

Class: Cephalosporin

Route of Administration: Oral

Purpose of Submission

The applicant 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)].

These applications are regulated under 21 CFR 314.54 which allow an applicant to rely on the Agency's finding of safety and effectiveness for an approved, reference listed drug to the extent such reliance would be permitted under the generic drug approval provisions at Section 505(j) of the Act.

The NDA concerns a change in the strength of an oral suspension of cefixime to 100 mg/mL from 200 mg/5 mL. The review of this NDA relies on prior FDA determination of safety and effectiveness for the reference listed drug, Suprax[®]. It does contain the results of two bioavailability/bioequivalence studies the applicant would like to use to establish a clinical bridge to the reference listed drug (RLD) SUPRAX[®] Cefixime for Oral Suspension, USP, 200 mg/5 mL (ANDA #A065355).

(b) (4)

Background

Cefixime has been marketed in the U.S. for many years. The NDA for Suprax[®] (oral tablet) (NDA 50-621) and Suprax[®] (cefixime for oral suspension) (NDA 50-622) were both approved on April 28, 1989. The NDA for SUPRAX[®] Cefixime for Oral Suspension, USP, 200 mg/5 mL (NDA 65-355) was approved on April 10, 2007. Cefixime is currently manufactured by Lupin Limited worldwide. The applicant is seeking approval of a new concentration of SUPRAX[®] Cefixime for Oral Suspension, USP, 100 mg/mL for the same indications approved for SUPRAX[®] (cefixime tablets), USP, and SUPRAX[®] (cefixime for oral suspension), USP, 200 mg/5 mL. Those indications are as follows:

- Uncomplicated Urinary Tract Infections;
- Otitis Media;
- Pharyngitis and Tonsillitis;
- (b) (4) Acute Exacerbations of Chronic Bronchitis; and
- Uncomplicated gonorrhea (cervical/urethral)

The applicant requested a waiver of pediatric studies for the 100 mg/mL oral suspension. Efficacy and safety in infants less than six months of age has not been established. However, since the application for this drug product does not contain a new active ingredient, new formulation, new indication, new dosing regimen or new route of administration, no pediatric studies are required under the Pediatric Research Equity Act (PREA).

Chemistry and Manufacturing Controls

Drug Product Information

Proprietary Name: SUPRAX[®]

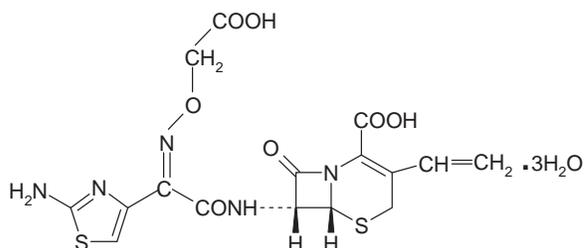
Established Name: Cefixime for Oral Suspension, USP

Dosage Form: Powder for oral suspension

Route of Administration: Oral

Cefixime USP

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, 7²-(*Z*)-[*O*-(carboxymethyl) oxime] trihydrate.

Chemical Structure:

Chemical Formula: $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$

Molecular weight = 507.50 as the trihydrate.

Dosage Strength: 100 mg/mL

Please see the CMC review by Dr. Andrew Yu, Ph.D., review chemist, for detailed descriptions of the drug product and manufacturing procedure. The active pharmaceutical ingredient in this product is cefixime which is obtained from LUPIN Ltd, Mumbai, India. The manufacturer has given right of reference to the drug master file #159961 for this drug product. Cefixime has a molecular weight of 507.50 as the trihydrate. The molecular formula is $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$. The drug substance cefixime USP specification contains (b) (4). According to the applicant, a qualitative visual test for description has been incorporated into the specification sheet to confirm that incoming batches of drug substance comply with the description. A highly specific test for identity has been incorporated whereby the drug substance is compared to the reference standard via IR spectroscopy. The applicant has not submitted any additional information concerning the physical or chemical description of the product, but refers to the information found in the labeling for the reference listed product.

Pharmacology/Toxicology Information

The pharmacology/toxicology review for this product was written by Dr. Amy Nostrandt, D.V.M., Ph.D., HFD-520 Pharm/Tox Reviewer. No new non-clinical pharmacology or toxicology information was included in the submission. The applicant refers to information found in the labeling for the reference listed drug, Suprax[®], in accordance with regulations found under 21 CFR 314.51(a)(3).

Clinical Pharmacokinetics and Biopharmaceutics

Please see the biopharmaceutics review written by Dr. Yongheng Zhou, Ph.D., Clinical Pharmacology Reviewer, for more details concerning the results of the two bioavailability/bioequivalence studies included in the submission.

The studies were as follows:

Study 312-07: A phase 1, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral bioequivalence study to compare the bioavailability and to characterize the pharmacokinetic profile of Suprax[®] Cefixime for Oral Suspension, 100 mg/mL with respect to SUPRAX[®] Cefixime for Oral Suspension USP, 200 mg/5 mL in healthy, adult subjects under fasting conditions and to assess the bioequivalence.

Study 313-07: A phase 1, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral bioequivalence study to compare the bioavailability and to characterize the pharmacokinetic profile of Suprax[®] Cefixime for Oral Suspension, 100 mg/mL with respect to SUPRAX[®] Cefixime for Oral Suspension USP, 200 mg/5 mL in healthy, adult subjects under fed conditions and to assess the bioequivalence.

According to the applicant, the Suprax[®] Cefixime for Oral Suspension, 100 mg/mL was shown to be bioequivalent to SUPRAX[®] Cefixime for Oral Suspension USP, 200 mg/5 mL when both were given at a dose of 200 mg cefixime to healthy adults under fasted (Study 312-07) and fed (Study 313-07) conditions. Since the clinical bridge has been established, the applicant is relying on the clinical studies conducted in support of the RLD Suprax. There were 48 healthy male volunteers who were administered a single dose of the test product (Cefixime 100 mg/mL oral suspension) and the reference product (Suprax 200 mg/5 mL oral suspension) in 2 different studies with 24 volunteers each. A washout period of 7 – 9 days were maintained between the 2 successive dosing periods.

The results of the two studies are shown in the following tables included in the submission. The 90% confidence intervals for the geometric mean test-to-reference for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were within the FDA bioequivalence acceptance range of 80 to 125% under both fasted and fed conditions.

**Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for
Cefixime under Fasted Conditions (N=24)
Study 312-07**

Parameters (units)	In-transformed data			90% Confidence Interval (Parametric)
	Geometric Least Squares Mean			
	B: Cefixime 100 mg/mL (fasted)	A Cefixime 200 mg/5 mL (fasted)	Ratio (B / A) %	
C_{max} (µg/mL)	3.636	3.283	110.8	104.23 – 117.71 %
AUC_{0-t} (µg·h/mL)	29.736	26.702	111.4	103.97 – 119.29 %
$AUC_{0-\infty}$ (µg·h/mL)	30.210	27.284	110.7	103.59 – 118.36 %

**Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for
Cefixime under Fed Conditions (N=24)
Study 313-07**

Parameters (units)	In-transformed data			
	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_{max} ($\mu\text{g/mL}$)	1.773	1.892	93.7	84.48 – 103.88 %
AUC_{0-t} ($\mu\text{g}\cdot\text{h/mL}$)	14.531	15.375	94.5	85.58 – 104.38 %
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	15.088	15.897	94.9	86.22 – 104.48 %

According to the applicant, the results of these two bioavailability/bioequivalence bridging studies demonstrated that the cefixime 100 mg/mL oral suspension is bioequivalent to the RLD (Suprax 200 mg/5 mL) when both were given at a dose of 200 mg cefixime to healthy adults under fasted (Study 312-07) and fed (Study 313-07) conditions.

The applicant has not provided any new clinical pharmacokinetic or biopharmaceutical statements to be added to the labeling. Therefore, the information found in the CLINICAL PHARMACOLOGY section of the label is taken from the label for the reference listed drug, SUPRAX[®].

Microbiology

On February 10, 2011, the applicant submitted an amendment that included 36 references from the Scientific/Medical literature concerning the effectiveness of cefixime in treating the various infections found in the Indications and Usage section. However, the additional information was not included for the purpose of making any changes to the Microbiology section of the labeling. Thus, the information found in the current labeling for the reference listed drug, SUPRAX[®] will be used, as permitted under 21 CFR 314.54(a)(3). Please see the microbiology review by Mr. Kerry Snow, HFD-520 Microbiologist, for additional details concerning the review of the references.

Clinical Data

Efficacy

The applicant has not included the results of any new clinical trials demonstrating efficacy of this product, but is relying on the previous finding of efficacy for the reference listed drug, SUPRAX[®]. The applicant did include a list of 18 references from the Scientific/Medical literature that contain both efficacy and safety data to support the application.

Clinical Reviewer's Comment: *The use of product information regarding indications from the labeling for SUPRAX[®] is permitted by provisions found under 21 CFR*

314.54(a)(3). *The information must be identical to that found with the reference listed drug.*

Review of references submitted by the applicant

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 gonorrhoea. **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. Dabernat, H., P. Geslin, F. Megraud, *et al.* 1998. Effects of cefixime or co-amoxiclav treatment on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. **J. Antimicrob. Chemother.** 41:253-258.

The article reports the results of a multi-center, open-label, randomized study that compared treatment with cefixime suspension (8 mg/kg/day) twice a day with co-amoxiclav (amoxicillin:clavulanate ratio 8:1 oral suspension, 80 mg/kg/day) three times a day for 10 days on the nasopharyngeal carriage of *Streptococcus pneumoniae* and *Hemophilus influenzae*. There were 426 children with nasopharyngeal cultures at entry to the trial, end of therapy, and at the follow-up visit. There were 214 children treated with cefixime and 212 with co-amoxiclav. There were significant changes in the carriage of *S. pneumoniae* with the proportion of penicillin-resistant strains higher in the samples taken at the end of treatment and follow-up than in those taken at inclusion. The difference at the end of treatment was greater with co-amoxiclav than with cefixime. For *H. influenzae*, the resistance rate remained steady while the number of children with this organism decreased. At follow-up there was no significant difference between the two groups in terms of nasopharyngeal positive culture for *S. pneumoniae* or *H. influenzae*.

Clinical Reviewer's Comments: *The paper focused on the effects of cefixime or co-amoxiclav treatment on the nasopharyngeal carriage of Streptococcus pneumoniae and Hemophilus influenzae. There were no reports of adverse events among the 501 pediatric out-patients enrolled in the study.*

5. Dagan, R., M. Einhorn, R. Land, *et al.* 1992. Once daily cefixime compared with twice daily trimethoprim/sulfamethoxazole for treatment of urinary tract infection in infants and children. **Pediatr. Infect. Dis. J.** 11:198-203.

The study described in the reference was a randomized, prospective, multi-center study to compare once daily cefixime (8 mg/kg) to twice daily oral trimethoprim/sulfamethoxazole (TMP/SMX) 8/40 mg/kg/day for the treatment of acute urinary tract infections in children ages 6 months to 13 years. Seventy-six patients were enrolled, with 38 in each group. Both treatment groups were treated for 7 to 10 days. There were no failures in either group; however, there were two relapses in the cefixime group and one in the TMP/SMX group. There were adverse events reported in 14% of the cefixime treatment group and in 16% of the TMP/SMX treatment group.

Clinical Reviewer's Comments: *Although the study was not large with only 76 patients, it did show once daily cefixime comparing favorably with TMP/SMX administered twice daily in the treatment of acute uUTI in children. Side effects were observed in 14% of the cefixime-treatment group and 16% of the TMP/SMX treatment group. All of the events were mild and there were no discontinuations of therapy.*

6. Gok, F., A. Duzove, Ee. Baskin, *et al.* 2001. Comparative study of cefixime alone versus intramuscular ceftizoxime followed by cefixime in the treatment of urinary tract infections in children. **J. Chemother.** 13:277-280.

The study reported in this paper compares the efficacy of oral cefixime to initial intramuscular ceftizoxime followed by cefixime for the treatment of UTI in children. Fifty-four children were randomized to receive either oral cefixime (8 mg/kg/day) for 10

days or initial IM ceftizoxime (cefizox) 50 mg/kg twice a day for 2 days followed by oral cefixime for 8 days. The demographics of the two treatment groups were comparable. No serious adverse events were observed. The cure rates were comparable in both treatment groups (92% versus 86% at the end of therapy).

Clinical Reviewer's Comments: *The results of the study showed the treatment group that received oral cefixime alone for 10 days had a higher cure rate than the group that received the ceftizoxime IM followed by oral cefixime for 8 days. It appears that there was no advantage to starting therapy with a parenteral drug and then switching to an oral preparation. The data also show cefixime to be effective in treating uUTI in children. The authors report there were no adverse effects on serum electrolytes, hemoglobin, hematocrit, and Coomb's test observed in either of the groups. Cefixime caused diarrhea in one patient which was not severe.*

7. 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.*

8. 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 all isolates of N. gonorrhoeae. The most common adverse events among patients receiving cefixime were headache (3%) and nausea (2%).*

9. Johnson, C.E., S.A. Carlin, D.M. Super, *et al.* 1991. Cefixime compared with amoxicillin for treatment of acute otitis media. **J. Pediatr.** 119:117-122.

The article concerns a study that compared cefixime to amoxicillin for the treatment of acute otitis media in a randomized trial involving 126 pediatric patients. There were 62 patients (mean age = 19.9 ± 3.5 months) in the amoxicillin-treatment group and 64 patients (mean age = 16.3 ± 2.2 months) in the cefixime-treatment group. Pathogen eradication occurred in 27 of 34 (79.4%) children given amoxicillin and in 26 of 30 (86.7%) children given cefixime ($p = 0.47$). When *S. pneumoniae* cases were analyzed, bacteriological eradication occurred in 14 of 15 (93.3%) children given amoxicillin compared to 12 of 16 (75%) children given cefixime ($p = 0.333$). When *H. influenzae* infections were analyzed, more cures occurred with cefixime (10/10, 100%) than with amoxicillin (8/13, 62%) ($p = 0.046$). There were 4 failures with cefixime therapy and all were in patients infected with *S. pneumoniae*. Adverse reactions including rash, diarrhea, and vomiting were the same in both treatment groups. The authors concluded the following: 1) that cefixime and amoxicillin were comparable in overall clinical and pathogen eradication for otitis media; 2) cefixime was more efficacious than amoxicillin in treating *H. influenzae* otitis media and should be the preferred drug of choice for this pathogen; and 3) side effects of both drugs were mild and equivalent.

Clinical Reviewer’s Comments: *The reference describes another study in which cefixime is shown to be an effective agent in treating otitis media among children. As seen in other studies, cefixime is more efficacious in eradicating H. influenzae than S. pneumoniae. The most common side effect noted was diarrhea, present in 29.4% of patients given amoxicillin and 33.9% of patients treated with cefixime. Four children had transient increases in alanine aminotransferase values during treatment. Two of these children were receiving amoxicillin and two, cefixime.*

10. 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.*

11. 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).

12. 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 IV, 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.*

13. 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.

Clinical Reviewer's Comments: *The authors did a good job in writing this review article.*

14. 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.*

15. Megran, D.W., K. Lefebvre, V. Willetts, *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.*

16. Miller, 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.

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

17. 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.*

18. 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 β -lactamase.

The most common adverse event was diarrhea noted in 6 patients in the cefixime-treatment group and none in the cephalexin-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 very questionable. The success rate for the cefixime-treated group was 95.8% compared to the success rate for the cephalexin 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 cephalexin 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 cephalexin (19 versus 5 episodes, respectively).

Safety

The applicant is relying on the previous finding of safety for the reference listed drug, SUPRAX[®]. Additional safety data found in the references from the literature was reviewed previously.

Search of FDA's Adverse Event Reporting System (AERS)

A computerized search of FDA's AERS was conducted for the purpose of identifying any recent changes in the safety profile for cefixime. The following parameters were used in the search: The active ingredient was cefixime; the trade name was Suprax; the event dates were for 5 years, March 17, 2006 to March 17, 2011; and the outcomes selected were death and life-threatening conditions.

The search retrieved 5 reports, with 2 deaths and 3 life-threatening situations. All of the reports were foreign. The cases involving the 2 deaths were examined for more information and the reports are summarized as follows: The first ISR report (#5892568) concerns a 40 year-old woman from Bangladesh who underwent a total abdominal hysterectomy for chronic cervicitis. After surgery she received cefixime, ranitidine, ceftriaxone, azithromycin and diclofenic. Doses for each medication and duration of therapy were not listed in the ISR report. The patient developed Stevens-Johnson Syndrome and mild anemia after taking cefixime, along with the other medications. The information was received from the following publication: Nur, J., F.R. Chowdhury, N. Ahasan, *et al.* Fatal outcome of Stevens-Johnson Syndrome (SJS) associated with Azithromycin(AZM). **Pakistan J. Med. Sci.** 2008; 24(3):455. Please see the reference for more details concerning this report.

Clinical Reviewer's Comments: *In the publication, the authors believe azithromycin to be the primary suspect drug because of the close temporal relationship between the administration of the drug and the onset of syndrome. The FDA reviewer lists cefixime as the primary suspect drug. Stevens-Johnson syndrome is listed as an adverse reaction in the labeling for both products. In the cefixime labeling, it is found in the section for events observed in clinical trials, while in the azithromycin labeling, it is listed under postmarketing experience.*

The second ISR report (#6553714) concerns a 63 year-old man from France who expired due to bone marrow failure after receiving 10 medications including Oroken (cefixime), total dose 400 mg. The primary suspect drug was listed as ciprofloxacin, while cefixime was considered a secondary suspect drug, along with Temodal and Solupred.

Concomitant medications included: Mopral (omeprazole), Pyostacine, Vancomycine, Amiklin (amikacin sulfate), and Fortum (ceftazidime).

Medication error

The Applicant currently markets two concentrations of cefixime suspension; 100 mg/5 mL (20 mg/mL) and 200 mg/5 mL (40 mg/mL). The suspension proposed in this NDA is of higher concentration, containing 100 mg/mL of cefixime and is 2.5 and 5 times more concentrated than the currently marketed 200 mg/5 mL and 100 mg/5 mL suspensions, respectively. The availability of three different concentrations of cefixime suspension increases potential for medication dispensing error related to suspension strength.

Accuracy and reliability of administered dose

The second safety concern related to this concentration of suspension is the ability to accurately and reliably administer small doses especially to young pediatric patients of low body weight.

(b) (4)

The following pediatric dosing table and information was included in the proposed product labeling.

(b) (4)

(b) (4)

(b) (4)

Because of the concerns regarding potential inaccurate dose administration with the more concentrated formulation, the Division scheduled a teleconference with the applicant to discuss concerns regarding the drug concentration (b) (4). This teleconference was held on April 13, 2011. The Division provided pre-meeting questions to which the applicant responded. The applicant provided conflicting responses about the target population for this concentration of suspension (100 mg/mL). Their stated rationale in developing the more concentrated product was for convenience and ease of administration of a smaller volume of liquid to younger patients (corresponding to the dosing chart found in the label). However, the applicant also stated that the target population was the pediatric population weighing more than (b) (4) kg, implying that the product would be used in older children. The applicant stated it had not made a decision regarding whether the less concentrated suspensions would remain on the market.

(b) (4)

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted because of the concerns regarding potential for drug product confusion (mix-up) with three different concentrations of suspension available on the market and ability to deliver an accurate and reliable dose. The review by DMEPA is pending at this time.

Discussion

The applicant has submitted a new drug application for the purpose of marketing a new, higher concentration of Suprax, cefixime for oral suspension 100 mg/mL. In addition, the applicant plans to include an unspecified, (b) (4) in the package insert. In support of this application, the results of two bioavailability studies were included.

During the review of this application, several significant problems became apparent. The

(b) (4)

A second major problem was the possibility for serious medical errors due to similarities between the 100 mg/mL product and two other, currently marketed concentrations of this oral suspension. The applicant would not commit to discontinuing the production of either the 100 mg/5 mL product or the 200 mg/mL product. Serious medical problems were anticipated with these three different concentrations available at the same time.

A third major factor was the doses could be given either as a full dose once a day or half of the dose given twice a day. (b) (4)

After the numerous communications with the applicant and a discussion with FDA personnel from DMEPA, it was decided that NDA 202,091 could not be approved in its present form.

Recommendation

It is recommended that NDA 202,091 not be approved at this time. The applicant should be sent a Complete Response letter outlining the reasons for not approving the application.

List of References from the Literature

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/s/

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