CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202091Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	February 4, 2013
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	202091
Applicant	Lupin Pharmaceuticals, Inc.
Date of Submission	August 17, 2012 (Received August 20, 2012)
PDUFA Goal Date	February 20, 2013
Proprietary Name / Established (USAN) names	Suprax® (cefixime)
Dosage forms / Strength	500 mg/5 mL – Powder for Oral Suspension
Proposed Indication(s)	For the treatment of uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral)
Recommended:	Approval

1. Introduction

In October 2010, Lupin Pharmaceuticals, Inc. submitted a 505(b)(2) NDA application for a new strength of Suprax® (cefixime) powder for oral suspension. Once reconstituted, the oral suspension would provide 500 mg/5 mL (100 mg/mL) of cefixime. The 505(b)(2) application included two bioequivalence studies comparing the proposed 500 mg/5 mL suspension with a lower strength (200 mg/5 mL) suspension. A complete response (CR) letter was issued for this NDA application on August 26, 2011. The background section below describes the deficiencies identified in the complete response letter.

The resubmission of the 505(b)(2) NDA application was received on August 20, 2012. The resubmission included responses to the deficiencies and other information requests in the complete response letter. This memo focuses on the reviewer findings for the resubmission of this NDA application.

2. Background

Cefixime is a cephalosporin antibacterial drug first marketed in the United States as oral tablets in 1986 and with a powder for oral suspension in 1989. Cefixime was marketed under the proprietary name Suprax by Lederle Laboratories for many years. Subsequently, Lupin Pharmaceuticals, Inc. acquired rights to the proprietary name, Suprax. Lupin Pharmaceuticals, Inc. markets several formulations of cefixime, including 400 mg tablets and capsules, and 100 mg/5 mL and 200 mg/5 mL powders for oral suspension. Of note, Suprax 400 mg capsules were recently approved under a separate 505(b)(2) NDA #203,195.

As noted in the introduction, Lupin Pharmaceuticals, Inc. submitted this 505(b)(2) NDA application for a higher strength suspension formulation (100 mg/mL) in 2010 and received a CR letter on August 26, 2011. The deficiencies cited in the complete response letter raised concerns about the potential for medication errors from two main sources. First, the description of the proposed higher strength suspension product as a 100 mg/mL suspension raised concerns about potential confusion with the applicant's existing 100 mg/5 mL suspension. To address this deficiency, the applicant was asked to revise the description of the product in labeling (carton and container labeling as well as the package insert) to identify the proposed product as a 500 mg/5 mL powder for oral suspension. This would highlight that the proposed product is higher strength than the currently marketed products (100 mg/5 mL and 200 mg/5 mL). The sponsor was also asked to conduct a human factors study to show that that "differentiation of the strength and the use of other label enhancements are effective in minimizing the risk of confusion between" the proposed and existing suspension products.

(b) (4)

Although not cited as deficiencies, there were several product quality information requests in the CR letter. These information requests asked for information related to the fill weight, overfill, volumes after reconstitution, moisture analysis for the drug product, reactivity with sodium benzoate, and recommended changes for the drug product specification.

The resubmission addressed the deficiencies in the CR letter and provided responses to the information requests from the product quality reviewer. The applicant responses are addressed in the "Other Relevant Regulatory Issues" and "Labeling" sections of this memo.

3. CMC/Device

The CMC reviewer for the NDA resubmission was Dr. Lin Qi. The reviewer recommended "approval pending team review and acceptance of labeling". There was sufficient information in the NDA to assure the identity, strength, purity and potency of the proposed product. There were no recommended postmarketing commitments or risk management steps from the CMC review.

As noted in the previous section of this memo, there were multiple CMC information requests relayed to the applicant in the CR letter. The applicant provided responses to the information requests in the NDA resubmission. The main body of Dr. Qi's CMC review for the resubmission goes over each of the responses to the information requests. The applicant's responses were considered acceptable. Of note, the applicant included a (b) (4) (based

on the (b) (4) method) in the drug product specification, and tightened other acceptance criteria in the drug product specification as recommended.

- General product quality considerations

  Drug Substance: The NDA applicant, Lupin Pharmaceuticals, Inc. is also the DMF holder for the cefixime drug substance. The DMF (15996) is current and adequate.

  Drug Product: The proposed drug product contains 500 mg/5 mL of cefixime after reconstitution. The final product is an off-white to cream colored powder that forms an off-white to pale yellow suspension when reconstituted. The powder is packed in HDPE (3 mL, 10 mL, and 20 mL) bottles.

- Facilities review/inspection

  An acceptable site recommendation was issued by the office of compliance.

- Other notable issues (resolved or outstanding)

  None

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review for the initial NDA application was Dr. Amy Nostrandt. She wrote a brief memo to the file for the initial application that mainly described proposed label changes to sections 8.1 Pregnancy and 13 Nonclinical Toxicology. The reviewer proposed changes to the numbers in these sections of the label to present dose multiples normalized for total body surface area. These proposed changes have already been incorporated in the proposed label for the recently approved Suprax 400 mg capsules under NDA 203,195, and the proposed oral suspension product will also be included in the same labeling for all Suprax products marketed by Lupin Pharmaceuticals, Inc.

There was no pharmacology/toxicology review for the resubmission, since the application did not include any non-clinical studies.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Zhixia Yan wrote a brief clinical pharmacology review memo for the resubmission, since there were no new clinical pharmacology studies conducted for the resubmission. The application was considered acceptable from the clinical pharmacology perspective. The clinical pharmacology review for the initial NDA submission was conducted by Dr. Yongheng Zhang. Briefly, the applicant conducted two bioequivalence (BE) studies (one under fed and one under fasted conditions) comparing the proposed 500 mg/5 mL suspension with the

approved 200 mg/5 mL suspension. The reviewer concluded that bioequivalence of the two suspensions had been demonstrated. The clinical pharmacology information provided by the applicant was considered adequate. The reader is referred to the review by Dr. Zhang for detailed information about the BE studies. These tables show the results for the BE studies comparing the proposed 500 mg/5 mL product (B) with the approved 200 mg/5 mL oral suspension (A).

Study 312-07 Results (Fasted)

Parameters (Units)	ln-transformed data			
	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fasted)	A: Cefixime 200 mg/5 mL (fasted)	Ratio (B / A)%	
C_{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

Study 313-07 Results (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%
$AUC_{0-\infty}$ (µg*h/mL)	15.088	15.897	94.9	86.22 - 104.48%

Source: Study 313-07 Final Report

6. Clinical Microbiology

Cefixime is a cephalosporin antibacterial drug. The clinical microbiology reviewer for the initial NDA application was Kerry Snow. There was no new clinical microbiology information provided in the initial submission or the resubmission. The reviewer concluded that the application could be approved, relying on FDA's previous findings for marketed cefixime products.

7. Clinical/Statistical- Efficacy

The clinical review of the initial submission was conducted by Mr. James Blank. The resubmission was reviewed by Dr. Dmitri Iarikov. Dr. Daniel Rubin was the statistical reviewer for both the initial application and the resubmission.

No new clinical studies were submitted for this 505(b)(2) application. The applicant is relying on FDA's previous findings of safety and effectiveness for cefixime to support the application for this higher strength suspension. The applicant did include 18 publications from the medical literature, which were reviewed by Mr. Blank in the clinical review of the initial NDA. The review of these studies did not alter Mr. Blank's view of the application as relying on FDA's previous findings of safety and effectiveness for approved cefixime products. The publications generally provided supportive information regarding the effectiveness of cefixime for the approved indications, and reported adverse reactions already listed in the approved product label for cefixime.

However, Mr. Blank cited concerns regarding the potential for medical errors based on confusion between the proposed product (100 mg/mL) and the approved 100 mg/5 mL and 200 mg/5 mL suspensions. For example, confusion between the 100 mg/mL proposed product and the 100 mg/5 mL suspension could result in 5-fold differences in the intended and administered doses.

(b) (4)

No additional efficacy information was provided in the resubmission. Dr. Iarikov's review of efficacy simply notes that the applicant is relying on FDA's "previous finding of efficacy for cefixime products". Dr. Iarikov recommended approval of the application.

8. Safety

The applicant is relying on FDA's previous findings of safety for cefixime products to support the safety of the proposed 500 mg/5 mL product. The clinical review of the initial NDA by Mr. James Blank and the clinical review of the resubmission both evaluated recent post-marketing adverse event (AE) reports for cefixime products. The review by Mr. Blank included an assessment of deaths or life-threatening AE reports between March 2006 and March 2011 to identify recent significant adverse reactions that could affect his conclusions about the product safety. His review described two foreign reports of deaths associated with use of cefixime. In both cases, there was another primary suspect medication as the cause of the adverse reactions (Stevens-Johnson syndrome and bone marrow failure); cefixime was considered a secondary co-suspect medication. Both Stevens-Johnson syndrome and pancytopenia are included in the cefixime label in the Adverse Reactions - postmarketing experience section.

The resubmission included a safety update reviewed by Dr. Iarikov. No new clinical studies of the proposed product were conducted by the applicant in the interim between the original NDA submission and the resubmission. The clinical review indicates that AE reports in a search of the AERS database conducted in October 2011 found AE reports "consistent with adverse events associated with the use of cephalosporins". A PubMed search identified two case reports of adverse reactions associated with cefixime. One report was for non-convulsive status epilepticus and the other was for hepatotoxicity (described as NCI toxicity grade 2 transient elevations of hepatic transaminases). The medical officer noted that both seizures and elevations of liver function tests are included in cefixime labeling, and do not represent unexpected adverse reactions. The cefixime label also includes hepatitis as a reported postmarketing adverse reaction.

(CDTL Comment: The reported safety findings from the initial NDA review and the resubmission do not provide additional safety issues that would alter FDA's prior conclusions about the safety of cefixime products.)

9. Advisory Committee Meeting

Not applicable. There was no advisory committee meeting for the proposed product.

10. Pediatrics

As noted previously, the applicant is relying on FDA's previous findings of safety and effectiveness for cefixime for approval of the proposed 500 mg/5 mL suspension. It should be noted that cefixime oral suspensions are approved for treatment of acute otitis media and labeled for pediatric patients as young as 6 months of age. Since the proposed product is a higher strength of an already approved oral suspension product, the provisions of the Pediatric Research Equity Act for pediatric study requirements of certain new drug products do not apply to the proposed 500 mg/5 mL oral suspension product.

11. Other Relevant Regulatory Issues

A consult review from the Division of Medication Error Prevention and Analysis (DMEPA) was conducted by Dr. Denise Baugh for the initial NDA application. Briefly, this review raised concerns regarding the potential for confusion from introduction of the proposed higher strength oral suspension. In the initial NDA application, the proposed product was labeled as a (b) (4) powder for oral suspension. The DMEPA review raised concerns about product confusion with the 100 mg/5 mL product in particular, because of the similar packaging and the similarity of the description of the concentration for the two products. The DMEPA review also raised concerns about the proposed (b) (4) . The reviewer was concerned that the (b) (4) and associated

(b) (4) for use could also contribute to "wrong dose errors". The DMEPA consult review conclusions and recommendations became the basis for the deficiencies cited in the CR letter issued in August 2011.

For the resubmission, the DMEPA consult review was conducted by Dr. Aleksander Winiarski. Dr. Winiarski reviewed the carton and container label changes and the user testing study submitted by the applicant. In the resubmission, the applicant did revise the carton and container labeling for the proposed product to describe the concentration as 500 mg/5 mL and make other changes to distinguish it from the 100 mg/5 mL product. The user testing study evaluated the ability of pharmacists and pharmacy technicians to identify the appropriate concentration and bottle size for a prescription when multiple cefixime oral suspension products were present on the shelf. The reviewer concluded that "pharmacists and technicians can differentiate and select the correct concentration or strength of the oral suspension".

(b) (4)

In the original NDA submission, the applicant provided certification (form FDA 3454) of no prohibited financial arrangements with investigators, and that the investigators had no significant financial interests to disclose. The investigators of the two BE studies were listed in the certification.

12. Labeling

(b) (4) the review team recommended that the applicant provide one package insert for all of the Suprax formulations marketed by Lupin Pharmaceuticals, Inc. Of note, the applicant already had an approved 400 mg capsule of cefixime (NDA 203,195 approved on June 1, 2012) with a unified package insert for all its marketed formulations (tablets, capsules and powder for oral suspension). The applicant added the 500 mg/5 mL strength and the chewable tablets in the package insert proposed for this application.

The main changes from the package insert for NDA 203,195 were the additions to the Dosage Forms and Strengths and How Supplied sections of the label. The review team recommended

changes to the Dosage and administration section to include a revised pediatric dosage chart and a new table of doses for adults with renal impairment.

(CDTL Comment: I proposed some changes to the pediatric dosage chart included in the DMEPA consult review, specifically to leave a blank in place of some mL amounts provided for use of the 200 mg/5 mL and 500 mg/5 ml oral suspension products in pediatric patients weighing between 5 and 10 kg. I made this recommendation because of the small volumes of these high concentration suspensions that would be needed for patients in this weight range, along with the difficulty of accurately measuring volumes in tenths of an mL. For example, to give a 5 kg infant the dose of 8 mg/kg/day divided twice daily, the patient would need to receive 0.2 mL of the 500 mg/5 mL suspension twice daily. Even a small inaccuracy in measurement of this 0.2 mL volume could cause a significant increase in the actual dose administered to the infant. For this reason, I considered it preferable for prescribers and pharmacists to need to calculate the correct weight-based dose of the higher concentration solutions for patients in this weight range. The table also states that the 100 mg/5 mL and 200 mg/5 mL suspensions are the preferred concentrations to use for patients in this weight range.)

The applicant has incorporated the review team's proposed changes in the package insert and container labeling. (b) (4) This is potentially problematic, because the user testing study tested the carton labeling. The applicant has agreed to continue packaging in the Appears This Way On Original

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of this 505(b)(2) NDA for Suprax 500 mg/5 mL powder for oral suspension.

- Risk Benefit Assessment

The proposed product is a higher concentration (500 mg/5 mL) powder for oral suspension of an already approved and marketed antibacterial drug, cefixime. The applicant is relying on FDA's previous findings of safety and effectiveness for cefixime products, and the demonstrated bioequivalence of the proposed product in comparison to the 200 mg/5 mL suspension. (b) (4) The recent publications and postmarketing adverse event reports for cefixime did not change the review team's conclusions about the basis for approval of this NDA.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

If this NDA application is approved, the applicant should be instructed to submit a labeling supplement for NDA 203,195 for Suprax (Cefixime) 400 mg tablets so that the labeling for the capsules will be the same as for the oral suspension. The applicant should also revise the labeling for their ANDA Suprax products accordingly.

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/s/

JOHN J ALEXANDER
02/19/2013