CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203195Orig1s000

SUMMARY REVIEW

Addendum to Deputy Division Director's Decisional Memo

Date	June 1, 2012
From	Katherine Laessig, M.D.
Subject	Deputy Division Director's Decisional Memo
NDA #	NDA 203-195
Applicant Name	Lupin Limited, c/o Lupin Pharma
Date of Submission	8/1/2011
PDUFA Goal Date	6/1/2012
Proprietary Name / Established (USAN) Name	Suprax®
Dosage Forms / Strength	Cefixime 400 mg capsules
Approved Indications	For the treatment of uncomplicated urinary tract infection, otitis media, pharyngitis and tonsillitis, acute exacerbations of chronic bronchitis, and uncomplicated gonorrhea (cervical/urethral)
Action:	Approval

Materials Reviewed/Consulted	**Names of discipline reviewers**
Cross-Discipline Team Leader Review	Kimberly Bergman, Pharm.D.
ONDQA Review	Maotang Zhou, Ph.D.
Clinical Review	Nasim Moledina, M.D.
Clinical Pharmacology Review	Assadollah Noory, Ph.D.

Addendum

Review of the label prior to taking the action revealed language regarding the otitis media indication, such that only the suspension is recommended for use based on PK/PD and the target population, which is primarily pediatric. Therefore, this indication has been removed from the action letter. It remains in the label for Suprax because this is a unified label for the 400 mg tablet, 400 mg capsule, and two suspensions. However, the caveat to use only the suspension for the otitis media indication is described in Dosage and Administration.

Katherine A. Laessig, M.D.

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/s/

KATHERINE A LAESSIG
06/01/2012

Deputy Division Director's Decisional Memo

Date	May 30, 2012
From	Katherine Laessig, M.D.
Subject	Deputy Division Director's Decisional Memo
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Applicant Name	Lupin Limited, c/o Lupin Pharma
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1.0 Background

Lupin Pharma has submitted this application for Suprax (cefixime) 400 mg capsules under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Cefixime was initially approved on April 28, 1989. Suprax is available as 400 mg tablets, and as 100 mg/5 mL and 200 mg/5 mL suspensions. The applicant is relying on the Agency's previous finding of safety and efficacy of Suprax, and has submitted a review of the published literature for cefixime. In addition, the applicant conducted Study LBC-10-044 which was an open label, balanced, randomized, single-dose, three-treatment, three-sequence, three-period crossover oral study to assess the bioequivalence of cefixime capsules 400 mg to cefixime tablets 400 mg under fasting and fed conditions in healthy adult

subjects and a complete study report is included in this submission. The RLD is Suprax 400 mg tablets, for which Lupin is the manufacturer.

Cefixime is a semi-synthetic, cephalosporin antibacterial drug that acts via inhibition of bacterial cell wall synthesis. Its approved indications are listed above.

This memo will summarize key findings of each review by discipline. This application has been reviewed by CMC, clinical pharmacology, and clinical reviewers. Note that there is no new pharmacology/toxicology, clinical microbiology, or efficacy information contained in this submission. For detailed discussion by discipline, please refer to the respective reviews.

2.0 Summary of Chemistry, Manufacturing, and Controls

This application was reviewed by Maotang Zhou, Ph.D. and is recommended for approval from a CMC perspective. Key findings of Dr. Zhou's review include:

- An "acceptable" overall site recommendation from the Office of Compliance has been made.
- The drug substance is manufactured by Lupin Limited in Mandideep, India and its CMC information is referred to DMF 15996. The holder DMF 15996 is also the applicant of NDA 203-195. DMF15996 is current and adequate.
- Suprax capsules 400 mg are size "00EL" capsules with dark brown cap and dark brown body imprinted with "LU" on cap and "U43" on body in white ink containing white to yellowish white granular powder. All of the excipients in the new formulation are of USP/NF grade and can be found in FDA's Inactive Ingredients Guide search for approved drug products at the same or higher amounts than the proposed drug product. The capsule shell meets acceptance specifications. The drug product is manufactured by Lupin Limited at Madhya Pradesh, India.
- The drug product specifications include description, identification, water content, dissolution, uniformity of dosage units, degradation products and assay, and microbial limits. The acceptance criteria are comparable to those of other FDA-approved cefixime formulations manufactured by the same applicant. The specifications have been (b) (4) according to FDA's recommendation during the NDA review and are deemed appropriate as revised.
- The commercial product will be packaged in 50 count HDPE bottles and the physician samples in 1 count blister packs. Stability information was provided for 3 lots of each. Capsules in the stability program were tested for description, assay, degradation products, dissolution, moisture of capsule contents, and microbial limits. An expiration dating of 24 months has been found to be acceptable based on the available stability data.

- The biopharmaceutics review found that the dissolution acceptance criterion, Q= (b) (4) % at 45 min, for the 400 mg capsule is acceptable, as is the dissolution method using USP Apparatus 1 (Basket) with a speed of 100 rpm.

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

3.0 Summary of Clinical Pharmacology

This application was reviewed by the clinical pharmacology reviewer, Assadollah Noory, Ph.D., and is recommended for approval from a clinical pharmacology standpoint. The CDTL, Kimberly Bergman, Pharm.D., concurs with this assessment. The conclusions from Dr. Noory's review of Study LBC-10-004 are:

- The 90% confidence limits for cefixime are within 80-125% for AUC and C_{max}, indicating that the capsule is bioequivalent to the tablet under fasting conditions.
- Food reduced cefixime exposure by 15% based on AUC and 25% based on $C_{max.}$
- There is an increased time to T_{max} from 5.06 hours to 6.45 hours (a 27% increase).
- An analysis of estimated T>MIC for subjects receiving cefixime capsule under fed and fasted conditions demonstrated similar estimated T>MIC values. Therefore, the capsule may be administered without regard to food intake.

4.0 Summary of Clinical Review

Based on the Agency's previous finding of safety and efficacy of cefixime for its labeled indications, the results of the BA/BE study submitted by the applicant, and the review of the available literature also provided by the applicant, the clinical reviewer, Nasim Moledina, M.D., recommends that this application be approved. Note that previously cefixime labeling included an indication for acute bronchitis. More recent studies published in the literature have not been able to demonstrate efficacy for this indication, and the applicant agreed to remove it from the package insert. Mr. James Blank conducted the review of the published literature and did not identify any new adverse events. The safety profile of cefixime is adequately described in the approved package insert.

5.0 Summary of Other Regulatory Issues

With this submission, the label has been converted to PLR format. The container, carton, and insert labeling were reviewed by DMEPA and their recommendations were conveyed to the applicant. The applicant made the changes and DMEPA concludes that the revisions are acceptable.

The label was also reviewed by the Division of Professional Promotion and their changes incorporated into the product labeling, as appropriate.

Cefixime is already labeled for the pediatric population 6 months of age and older. The pediatric study requirement for ages birth to less than six months is waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. The waiver is justified since most of the labeled indications do not occur or do not occur as uncomplicated conditions in this age group. For the indications (otitis media and pharyngitis) that do occur in this age group, the conditions are rare and Suprax would not provide a meaningful therapeutic benefit over existing treatments.

6.0 Regulatory Action

I concur with the findings of the review team that this application for Suprax 400 mg capsules may be approved under 505(b)(2) of the FD&C Act as the elements of that act have been met with the information and BA/BE study provided by Lupin.

Katherine A. Laessig, M.D.

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/s/

KATHERINE A LAESSIG
06/01/2012