

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202091Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number: NDA 202091, SDN 10, eCTD Sequence Number 0007

Drug Name: Suprax[®] Cefixime for Oral Suspension, 100 mg/mL

Indication(s): Uncomplicated urinary tract infections, otitis media, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, uncomplicated gonorrhea (cervical/urethral)

Applicant: Lupin Limited

Stamp Date: August 20, 2012

PDUFA Date: February 20, 2013

Review Priority: Standard

NDA Type: 505(b)(2), Resubmission/Class 2

Biometrics Division: Division of Biometrics IV

Statistical Reviewer: Daniel Rubin, PhD

Concurring Reviewers: Thamban Valappil, PhD

Medical Division: Division of Anti-Infective Products

Medical Officer: Dmitri Iarikov, MD

Clinical Team Leader: John Alexander, MD

Project Manager: Christopher Davi

1 SUMMARY

On October 25, 2010 the Applicant, Lupin Limited, submitted New Drug Application 202091 for Suprax Cefixime for Oral Suspension, 100 mg/mL, utilizing the 505(b)(2) regulatory pathway. The reference listed drug (RLD) to support safety and efficacy was Suprax Cefixime for Oral Suspension USP, 200 mg/5 mL (ANDA #A065355) held by LUPIN PHARMS. The Applicant sought approval for the new formulation of a previously approved product with evidence of safety and efficacy provided by two bioavailability/bioequivalence studies, the Agency's previous findings of safety and efficacy for the RLD (Suprax), and safety and efficacy data from the published literature for cefixime. In reviewing this previous application this reviewer did not identify any statistical issues, but noted if the original cefixime application were now submitted for review it would not meet current scientific standards due to changes in regulatory thinking regarding noninferiority margins for indications such as uncomplicated urinary tract infections, otitis media, and (b) (4) acute exacerbations of chronic bronchitis, which would currently require superiority trials to demonstrate substantial evidence of efficacy. In August 2011 the Agency sent the Applicant a complete response letter regarding this NDA. In the current submission the Applicant has provided responses to deficiencies raised in this complete response letter, which can be summarized as follows:

- The Agency requested the concentration be revised from 100 mg/mL to 500 mg/5 mL to avoid confusion with a suspension currently marketed (100 mg/5 mL) to decrease the potential for dosing errors. The Applicant has complied with this revision, and updated container labels, carton labeling, and packaging so the new strength will be visually different from the currently marketed concentrations.
- The Agency requested the Applicant conduct Human Factors Testing, and the Applicant has conducted a Human Factor Testing Study. Review of this study is deferred to the reviewers from the Division of Medication Error Prevention and Analysis.

(b) (4)

- The Applicant updated the recommended dosage chart for the pediatric population.
- The Agency requested information regarding product quality. Review of the information provided by the sponsor is deferred to CMC and microbiology reviewers.
- The Agency requested a safety update, but in this submission the Applicant has replied that there have been no changes in the safety profile since the original NDA submission since it has not released any product for distribution nor conducted any clinical or nonclinical studies.

As with the original submission of NDA 202091, this reviewer did not identify any statistical issues in this resubmission. This reviewer therefore defers review of the updated labeling, Human Factors Testing, product quality information, and other responses from the Applicant to reviewers from other disciplines as summarized above.

2 CONCLUSION

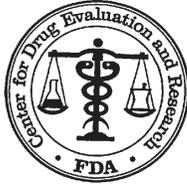
There are no new clinical studies in this application, and this reviewer has no statistical comments.

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/s/

DANIEL B RUBIN
09/20/2012

THAMBAN I VALAPPIL
09/20/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number: 202,091

Drug Name: Suprax[®] Cefixime for Oral Suspension, 100 mg/mL

Indication(s): Uncomplicated urinary tract infections, otitis media, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, uncomplicated gonorrhea (cervical/urethral)

Applicant: Lupin Limited

Stamp Date: October 27, 2010

PDUFA Date: August 27, 2011

Review Priority: Standard

NDA Type: 505(b)(2)

Biometrics Division: Division of Biometrics IV

Statistical Reviewer: Daniel Rubin, Ph.D.

Concurring Reviewers: Thamban Valappil, Ph.D.

Medical Division: Division of Anti-Infective and Ophthalmology Products

Medical Officer: James Blank, Ph.D.

Clinical Team Leader: Janice Pohlman, M.D., M.P.H.

Project Manager: Kyong Hyon

1 SUMMARY

The Applicant, Lupin Limited, has submitted a New Drug Application under the 505(b)(2) regulatory pathway for its product Suprax[®] Cefixime for Oral Suspension, 100 mg/mL.

The Applicant only proposes to change the concentration, and not the actual dose, of the reference listed drug SUPRAX[®] Cefixime for Oral Suspension USP, 200 mg / 5 mL, a generic product owned by LUPIN PHARMS and approved by the FDA in ANDA A065355.

Cefixime is an antibiotic in the cephalosporin class. The Applicant proposes to market its new formulation for the indications of uncomplicated urinary tract infections, otitis media, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, uncomplicated gonorrhea (cervical/urethral). These correspond to the FDA-approved indications for the reference listed drug.

The Applicant is seeking approval based on the following criteria:

- Bioavailability/bioequivalence studies to establish a bridge to the reference listed drug.
- The FDA's previous findings of safety and efficacy for the reference listed drug.
- Safety and efficacy data from the published literature for cefixime.

Review of the bioavailability/bioequivalence studies is deferred to the clinical pharmacology reviewer and to the medical officer. Review of safety data is deferred to the medical team. Although the Applicant has submitted published literature on efficacy, according to current regulatory standards the reliance on FDA's previous findings of efficacy for the reference listed drug is sufficient.

Statistical reviewer comment:

- *For the indications of uncomplicated urinary tract infections, otitis media, and acute bronchitis and acute exacerbations of chronic bronchitis, the current thinking of the Agency, as reflected in the guidance documents, is that the historical evidence of treatment effect does not support any scientifically justified non-inferiority margin, and that demonstrating substantial evidence of efficacy requires adequate and well-controlled superiority trials. Although the innovator drug was approved before the changes in our current scientific standards, the 505(b)(2) regulatory pathway allows the Applicant to rely on the prior efficacy findings. If the original cefixime application were submitted today for review, it would not meet the current efficacy standards.*

2 CONCLUSION

Based on the 505(b)(2) application, this reviewer has no statistical comments to report at this time.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Daniel Rubin, Ph.D.

Concurring Reviewers: Thamban Valappil, Ph.D., Statistical Team Leader

cc:

Division Director, Division of Biometrics IV/Mohammad Huque

Deputy Division Director, Division of Biometrics IV/Daphne Lin

Mathematical Statistician/Lillian Patrician

Project Manager/Kyong Hyon

Medical Officer/James Blank

Clinical Team Leader/Janice Pohlman

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/s/

DANIEL B RUBIN
03/01/2011

THAMBAN I VALAPPIL
03/01/2011