CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-157

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	January 28, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-157
Applicant Name:	UCB, Inc.
Date of Submission:	March 27, 2007
PDUFA Goal Date:	January 28, 2008
Proprietary Name:	Xyzal
Established Name:	Levocetirizine dihydrochloride
Dosage form:	Oral solution
Strength:	2.5 mg/5mL (0.5 mg/mL)
Proposed Indications:	Seasonal and perennial allergic rhinitis Chronic idiopathic urticaria
Action:	Approval

1. Introduction

UCB, Inc., submitted this 505(b)(2) application for use of Xyzal oral solution for relief of symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) and treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) for ages 6 years and older. Xyzal tablet was approved for the same indication and for the same ages on May 25, 2007 (NDA 22-064). The current application is to introduce a new dosage form. The applicant's rationale for developing levocetirizine oral solution is that liquid dosage forms are well-suited for use by children, elderly, and patients with dysphagia. This application is based on a clinical pharmacology program designed to showed bioequivalence between the tablet formulation and the oral solution formulation.

2. Background

Levocetirizine is a H1-receptor antagonist, and it is the R enantiomer of the racemate cetirizine. Cetirizine in various dosage forms is approved for marketing in the United States for symptomatic treatment of SAR, PAR, and CIU. Levocetirizine is also approved for marketing in the United States and in many other countries for similar indications. These indications are typical for H1-receptor antagonists.

3. Chemistry, Manufacturing, and Controls

Xyzal oral solution is formulated as an immediate release liquid in various compendial excipients. The CMC review team had concluded that the quality of the drug substance, drug product, and the container closure system are acceptable, and I concur with the

conclusion. All manufacturing and testing facilities associated with this drug product have acceptable EER status. Stability testing supports an expiry of 24 months.

4. Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology assessment is primarily based on findings of cetirizine tablets (NDA 19-835). No new non-clinical toxicology studies were required or performed for this application.

5. Clinical Pharmacology and Biopharmaceutics

Levocetirizine clinical pharmacology program consisted of one bioequivalence study (study A00318) conducted in 24 healthy subjects. This study showed that 5 mg (10 mL of 0.5 mg/mL) oral solution of levocetirizine is bioequivalent to 5 mg oral tablet (Table 1). Demonstration of bioequivalence of the oral solution to the approved reference product, Xyzal tablet (NDA 22-064), supports approval of this application.

Table 1. Mean PK parameters for levocetirizine, Study A00318

	Levocetirizine Tablets (5 mg)	Levocetirizine Oral Solution (5 mg)	Ratio (90% CI)
AUC 0-inf, ng.hr.mL	2004	2020	100 (96, 104)
Cmax, ng/mL	208	227	109 (102, 117)
Tmax, hr	0.67	0.50	

6. Clinical Microbiology

Not applicable

7. Clinical and Statistical – Efficacy

No clinical studies were required or conducted to support this application. The program was based on clinical pharmacology program as discussed above. The efficacy findings from the tablet formulation of levocetirizine are applicable to this product.

8. Safety

Safety finding from the oral tablet formulation are applicable to this product. No formulation specific safety issues are anticipated because this is a typical immediate release formulation.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Levocetirizine is currently approved for patients 6 years of age and older and there are no issues with the new dosage form that warrant discussion at an advisory committee meeting.

10. Pediatric

The Division considers that SAR does not exist or difficult to diagnose below 2 years of age, and PAR and CIU does not exist or difficult to diagnose below 6 months of age. Therefore, the applicant will need to conduct studies in children 2 to 6 years of age to support SAR indication, and in children 6 months to 6 years of age to support PAR and CIU indications. These studies will likely be pharmacokinetic studies to identify age appropriate dose, and safety studies to support safety of the selected doses or doses in the indented population. The applicant intends to conduct studies in pediatric patients 6 months to 6 years of age. These will become required post-marketing commitment studies. Studies in children under 2 years of age with SAR and in children under 6 months of age with PAR or CIU are waived.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was requested for this application. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements.

c. Others

There are no outstanding issues with consults received from DDMAC, DMETS, DSCRS, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the proprietary name Xyzal was reviewed during approval of NDA 22-064 for levocetirizine tablet and was found to be acceptable.

b. Physician Labeling

The labeling of Xyzal was reviewed in 2007 with approval of NDA 22-064 for levocetirizine tablet. With this application the existing label has undergone some minor changes to include information about the oral solution dosage form. The changes primarily affect the following sections: dosage and administration, dosage forms and strengths, description, clinical pharmacology, and how supplied/storage and handling. The label has been reviewed by various discipline of this Division, and also by DMETS, DDMAC, and SEALD, and found to be acceptable.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, and DMETS, and found to be acceptable.

d. Patient Labeling and Medication Guide

The patient counseling information were reviewed by various disciplines of this Division and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Xyzal oral solution 2.5 mg/5 mL (0.5 mg/mL) for relief of symptoms associated with SAR and PAR, and treatment of uncomplicated skin manifestations of CIU in patients 6 years of age and older. The action on this application will be Approval.

b. Risk Benefit Assessment

Overall risk and benefit assessment of levocetirizine support its approval without any specific marketing or labeling restrictions. Levocetirizine is a typical second-generation H1-receptor antagonist and its efficacy and safety profile is comparable to the racemate cetirizine. Like cetirizine, levocetirizine is sedating and carries warning to avoid engaging in hazardous occupations requiring mental alertness such as driving or operating machinery when taking levocetirizine. Unlike cetirizine, levocetirizine is recommended to be dosed in the evening. Even with evening dosing in clinical trials levocetirizine was sedating. Although levocetirizine is approved as a prescription drug in the United States, it is anticipated that like other second-generation H1-receptor antagonists, levocetirizine will move to over-the-counter status after a reasonable post-marketing experience. Allowing some time to gather post-marketing data is reasonable because all clinical trials that supported approval of cetirizine tablet were conducted outside the United States.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

Pediatric studies as discussed in Section 10 above.

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/s/

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