SUMMARY REVIEW OF REGULATORY ACTION

Date:	August 21, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-064, SE 05, S-017; and 22-157, SE 05, S-003
Applicant Name:	UCB, Inc.
Date of Submission:	February 25, 2009
PDUFA Goal Date:	August 25, 2009
Proprietary Name:	Xyzal
Established Name:	Levocetirizine dihydrochloride
Dosage form:	Tablets and oral solution
Strength:	5 mg tablets, 2.5 mg/5 mL (0.5 mg/mL) oral solution
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) in patients 6 months to 5 years of age. Xyzal tablet was approved for the same indication for patients 6 years and older on May 25, 2007 (NDA 22-064). Xyzal oral solution was approved for the same indication and same age group on January 28, 2008 (NDA 22-157). The current application is to extend the age range of approval down to 2 years for SAR and 6 months for PAR and CIU. The application is based on a clinical pharmacology program for dose selection and supported by a clinical safety program.

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.

With the original NDA submissions for Xyzal, the applicant proposed to seek indication down to 2 years of age based on already conducted pediatric studies. The original approval was for patients 6 years of age and older because most of the submitted data for children below 6 years of age were from diseases other than SAR, PAR, and CIU, the demographics were not representative of the entire age range of children for whom the indications were sought, and in those studies a weight-based dose was used rather than the proposed age-stratified fixed-dose. At a subsequent meeting, the Division

recommended that the applicant conduct a clinical pharmacology program to justify a dose or doses for children 6 month to 5 years of age, and conduct safety studies in age groups 6 months to 11 months and 12 months to 5 years. The Agency issued a Written Request on February 3, 2009, outlining these studies. The current submission is in response to that written request. This submission also satisfies the PREA requirements.

In addition to the Xyzal tablet and solution formulations mentioned above that are approved for marketing in the United States, (b) (4)

3. Chemistry, Manufacturing, and Controls

Xyzal 5 mg tablets and 2.5 mg/5 mL (0.5 mg/mL) oral solution are approved marketed products and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original NDAs.

5. Clinical Pharmacology and Biopharmaceutics

The applicant did not conduct any new dedicated clinical pharmacology studies to support this application. The relevant data submitted were retrospective population pharmacokinetic analyses from 9 previous studies in adults and children, and a supplemental population pharmacokinetic analysis that incorporated data from the two clinical safety studies in age groups 6 months to 11 months and 12 months to 5 years conducted to support this application.

Based on the population pharmacokinetic analysis, the applicant proposed 1.25 mg twice daily regimen for children 12 months to 5 years of age and 1.25 mg once daily regimen for patients 6 months to 11 months of age. This is in contrast to both the racemate cetirizine and Xyzal, both of which are initially dosed once a day for all indications in all age groups. The current dose of Xyzal for patients 6 to 12 years of age is 2.5 mg once daily.

The Agency reviewed the submitted data and conducted its own simulation and explored several dose and dosing regimens (once daily vs. twice daily). The Agency analysis concluded that the dose should be 1.25 mg once daily for patients 6 months to 5 years of age. For patients 12 months to 5 years of age, 2.5 mg once daily exceeded the range of Cmax concentrations in adults receiving 5 mg once daily dose. For the same age, with 1.25 mg twice daily, the 95th percentile of the Cmin values exceeded the Cmin range in adults who received 5 mg once daily. In contrast, with 1.25 mg once daily, the median Cmax and Cmin values fell within the adult range (5^{th}-95^{th} percentile) and the 95th percentile for both Cmax and Cmin values did not exceed the corresponding adult values.

For patients 6 months to 11 months of age, the Agency analysis supported 1.25 mg once daily regimen, which was confirmed by the applicant. The applicant agreed with the Agency analysis and the 1.25 mg once daily dosing regimen across the age ranges covered in this application.

6. Clinical Microbiology

The final product is not sterile, which is acceptable for an orally administered product. The manufacturing process is adequate from a microbiological perspective.

7. Clinical and Statistical – Efficacy

No clinical studies were required or conducted to support efficacy. The entire program was based on clinical pharmacology studies as discussed above. This is acceptable because of demonstrated efficacy of Xyzal in patients 6 years of age and older in the same diseases.

8. Safety

The safety assessment of Xyzal for 6 months to 5 years is based on two controlled safety studies conducted specifically to support this application (Table 1), other studies conducted by the applicant for the relevant ages, post-marketing surveillance reports in young children (levocetirizine is approved outside the United States in children below 6 years of age), and from the published literature for the racemate cetirizine.

In the two safety studies (Table 1) the applicant used (b) (4) (oral "drop", 5 mg/mL) (b) (4) This is acceptable because there is a link between the 5 mg/mL and the 0.5 mg/mL products as both have demonstrated bioequivalence to Xyzal 5 mg tablets. Furthermore, the two liquid formulations are simple solutions and could allow comparison without the need to conduct a bioequivalence study between the two liquid formulations.

Review of the safety data showed findings consistent with the findings in older children and adults. There were no new or unique safety findings seen in patients 6 months to 5 years of age.

Table 1. Clinical safety studies

ID	Study type	Study duration	Patient Age	Treatment groups*	N (ITT)	Study Year#	Countries
A00423	Safety	14 day	6-11 month	Xyzal 1.25 QD AM Placebo	45 24	2008	USA
A00426	PD, cross-over	Single dose	1 – 5 year	Xyzal 1.25 QD AM Placebo	114 59	2008	USA
* Xyzal = Xyzal 5 mg/mL oral drops # Year study subject enrollment ended							

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Levocetirizine and its racemate, cetirizine, have been studied in pediatric patients and the safety and efficacy of these drugs and antihistamines in general in SAR, PAR, and CIU are well understood. The findings from the submitted program were fairly obvious and did not 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, at the time of the previous Xyzal NDA review it was decided that the applicant would need to conduct studies in children 2 to <6 years of age to support the SAR indication, and in children 6 months to <6 years of age to support the PAR and CIU indications. The minimal required program was to include pharmacokinetic studies to identify an age appropriate dose, and safety studies to support safety of the selected doses or doses in the indented population. A Written Request encompassing these studies was issued on February 3, 2009. The current submission is in response to that written request. A final decision by the Pediatric Exclusivity Board whether the submitted studies meet the term of the Written Request is pending. This submission was discussed at the Pediatric Exclusivity Review Committee (PeRC) on July 27, 2009. This submission satisfies PREA requirement, and there are no outstanding pediatric study needs.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was conducted for this application because Xyzal has a known efficacy and safety profile in adults and pediatric patients 6 years of age and older. During review of this 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. There are no issues with financial disclosure in the studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC, DMEPA, 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 and in 2008 with approval of NDA 22-157 for levocetirizine oral solution. With this application the existing label has undergone some changes to include information about the new age group of 6 month to 5 years. The changes primarily affect the indication and usage, dosage and administration, and clinical pharmacology sections. The label has been reviewed by various discipline of this Division, and also by DMETS, DDMAC, and found to be acceptable.

c. Carton and Immediate Container Labels

No carton or immediate container labeling were submitted with this application.

d. Patient Labeling and Medication Guide

There is no separate patient instruction for use or medication guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Xyzal for relief of symptoms associated with SAR and PAR, and treatment of uncomplicated skin manifestations of CIU in patients 6 months to 5 years of age. The action on this application will be Approval. This action will apply both to NDA 22-064 for Xyzal tablet and NDA 22-157 for Xyzal solution because there is one unified product label for both dosage forms. The dosage and administration section recommends the Xyzal solution formulation for patients 6 months to 5 years of age.

b. Risk Benefit Assessment

Overall risk and benefit assessment of levocetirizine support its approval for patients 6 months to 5 years of age 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 a 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

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
08/21/2009