# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-157**

# MEDICAL REVIEW(S)

Safety Update/Addendum to Clinical Team Leader Secondary Review

NDA 22 – 157 (Xyzal Oral Solution)
Sponsor: UCB:
Submission stamp date: March 28, 2007
PDUFA date: January 28, 2008
Date of Addendum: January 25, 2008

The Applicant did not submit and the Division did not request a safety update for this application. The application for Xyzal tablets (NDA 22-064) was under review at the time this NDA 22-157 was submitted. The safety database included in NDA 22-064 included safety information from 44 completed studies from outside the U.S., and the 120-day safety update for that NDA included data from 3 recently completed studies, as well as post-marketing reports to the UCB global Drug Safety database not previously submitted in the original NDA application. (See Primary Medical Officer Review NDA 22-064). The data from that 120-day Safety Update did not identify any new safety issues. In view of the proximity of these two submissions, and with no clinical studies ongoing with levocetirizine oral solution, a 120-day Safety Update for this application was not necessary.

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/s/
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Lydia McClain
1/25/2008 10:57:25 AM
MEDICAL OFFICER

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 22-157 |
| Submission Code | |
| | |
| Letter Date | March 27, 2007 |
| Stamp Date | March 28, 2007 |
| PDUFA Goal Date | January 28, 2008 |
| | |
| Reviewer Name | Robert M. Boucher, MD, MPH |
| Review Completion Date | October 4, 2007 |
| | |
| Established Name | Levocetirizine dihydrochloride |
| (Proposed) Trade Name | Xyzal® |
| Therapeutic Class | Antihistamine |
| Applicant | UCB, Inc. |
| | |
| Priority Designation | S |
| | |
| Formulation | 0.5 mg/mL oral solution |
| Dosing Regimen | 2.5 mg or 5 mg once daily |
| Indication | SAR, PAR, CIU |
| Intended Population | Six years and older |

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## List of Abbreviations

| | |
|---|---|
| BA | bioavailability |
| BE | bioequivalence |
| CIU | chronic idiopathic urticaria |
| LCTZ | levocetirizine dihydrochloride |
| PAR | perennial allergic rhinitis |
| PK | pharmacokinetics |
| SAR | seasonal allergic rhinitis |

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

The recommended regulatory action for levocetirizine 0.5 mg/mL oral solution is approval, from a clinical standpoint, for the relief of symptoms associated with seasonal and perennial allergic rhinitis, and for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria, in patients 6 years of age and older.

The primary basis for approval of NDA 22-157, in addition to reference made to the approved NDA 22-064 (levocetirizine tablets, 5 mg), is a single bioequivalence study (A00318) that satisfactorily demonstrates the BE of LCTZ 10 ml (0.5 mg/mL) oral solution with LCTZ 5 mg oral tablet. Based on substantial evidence from replicate adequate and well-controlled clinical studies with levocetirizine 5 mg oral tablet, a review of which formed the basis of approval for NDA 22-064 for SAR, PAR, and CIU), levocetirizine is safe and effective for the label indications at a dose of 2.5 mg to 5 mg taken orally, once daily in the evening. In placebo-controlled studies of patients 6 years and older with seasonal and perennial allergic rhinitis, levocetirizine is effective in improving the total symptom score comprised of sneezing, rhinorrhea, nasal pruritus, and ocular pruritus. In placebo-controlled studies of patients 18 years and older with chronic idiopathic urticaria, levocetirizine is effective in improving the severity of pruritus, wheal number, and wheal size.

While placebo-controlled trials in the pediatric development program (ages 6 to 11 years) for NDA 22-064 using a dose of 5 mg once daily demonstrated that levocetirizine is effective in this age group, information on PK from literature cited in the application indicated that the systemic exposure (AUC) of levocetirizine 5 mg in pediatric patients 6 to 11 years of age is approximately twice that of adults, and supported LCTZ 2.5 mg as the appropriate dose for children 6 to 11 years of age.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The clinical review does not reveal the need for any risk management activity.

### 1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are sought for LCTZ oral solution.

## 1.3 Summary of Clinical Findings

With the exception of BE study A00318 no additional clinical trials were conducted to support NDA 22-157 and the applicant references the approved NDA 22-064 for pertinent clinical findings. Refer to section 1.3 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) for a summary of clinical findings.

### 1.3.1 Brief Overview of Clinical Program

The clinical program is comprised of one single-dose bioequivalence study in healthy volunteers designed to compare the bioequivalence of levocetirizine solution to levocetirizine oral tablets. Clinical efficacy and safety data for the proposed indications are referenced from NDA 22-064 (LCTZ 5 mg tablet).
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### 1.3.2 Dosing Regimen and Administration

The recommended dose is 2.5 mg ( 5 mL) once daily in the evening in children 6 to 11 years of age and 5 mg (10 mL) in adults and adolescents 12 years of age and older once daily in the evening

### 1.3.3 Drug-Drug Interactions

No formal drug-drug interaction studies with levocetirizine have been conducted. References of drug-drug interactions are to cetirizine the racemic mixture for which an interaction with probenicid has been reported. Refer to section 1.3.5 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet).

### 1.3.4 Special Populations

There are no safety or efficacy issues based on age, gender, or race with levocetirizine. Refer to section 1.3.6 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) for more details.

# 2 INTRODUCTION AND BACKGROUND

(USAN: levocetirizine dihydrochloride). Levocetirizine hydrochloride is the the R-enantiomer of the racemate cetirizine, is an $H_1$-receptor antagonist proposed for use in the symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU) in adults and children six years of age and older. The applicant has developed an oral solution Xyzal® 0.5 mg/mL oral solution for the same indication. The recommended dose is 2.5 mg (5 mL) in children 6 to 11 years of age and 5 mg (10 mL) once daily in adults and adolescents 12 years of age and older. An oral tablet formulation of levocetirizine dihydrochloride (Xyzal® tablets) was approved on May 25, 2007 (NDA 22-064).

UCB, Inc. submits NDA 22-157 for LCTZ 0.5 mg/mL oral solution under section 505(b)(2) referencing NDA 22-064 (LCTZ 5 mg oral tablet) for drug substance, nonclinical, biopharmaceutics and clinical data. The development program for levocetirinze solution is based on demonstration of bioequivalence of the oral solution to the oral tablet. With the establishment of bioequivalence, clinical efficacy and safety data are not required to support approval of the oral solution.

The applicant's rationale for developing LCTZ in an oral formulation is that liquid dosage forms are well-suited for use by children, the elderly, and patients with dysphagia.

## 2.1 Product Information

The product is an oral solution containing 0.5 mg/mL formulated with glycerin (b) (4) and maltitol (USP) as (b) (4) agents; sodium acetate, glacial acetic acid, and sodium acetate trihydrate as (b) (4) methylparaben and propylparaben as (b) (4) saccharin sodium as (b) (4); (b) (4) flavor (b) (4); and purified water as (b) (4)

## 2.2 Currently Available Treatment for Indications

Several products of the antihistamine class are available for the proposed indications. Refer to section 2.2 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) for a full list.

Currently marketed long-acting antihistamines available in liquid oral formulations include cetirizine, loratadine, desloratadine, and fexofenadine.

## 2.3 Availability of Proposed Active Ingredient in the United States

Levocetirizine dihydrochloride was approved for marketing in the on May 25, 2007. The product has not yet been launched.

## 2.4 Important Issues With Pharmacologically Related Products

Refer to section 2.4 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet).

## 2.5 Presubmission Regulatory Activity

The applicant requested a pre-NDA teleconference with FDA for January 26, 2007 (refer to meting minutes of that date for PIND 72,233). (b) (4) the applicant submits NDA 22-157 for a single oral liquid formulation, seeking the same age range and indications as the approved LCTZ 5 mg tablet, and references NDA 22-064 for clinical efficacy and safety data to support the current NDA.

## 2.6 Other Relevant Background Information

The applicant's LCTZ pediatric development plan (b) (4) includes a request for deferral of data submission for that population in NDA 22-157.

For additional relevant background information refer to section 2.6 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet).

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## 3.1 CMC (and Product Microbiology, if Applicable)

The CMC review for this NDA is by Dr. Craig Bertha who notes that the applicant references NDA 22-064 for all drug substance information and data.

From a CMC standpoint, the application is recommended for approval.

Levocetirizine oral solution is an aqueous-based product containing 0.5 mg LCTZ/mL formulated at a target pH of 5.0. The drug product is (b) (4) by sodium acetate/acetic acid and includes maltilol solution, glycerin, saccharin (b) (4) flavoring, and (b) (4) methyl- and propylparaben. The solution is packaged in 5 ounce amber glass (b) (4) bottles and is demonstrated to have adequate stability to support a 24 month shelf life.

(At the completion of this clinical review 2 CMC-related issues are pending: 1) daily exposure to leachables from the (b) (4) bottles [UCB commits to only dispensing LCTZ oral solution in the 15 mL and 150 mL in glass bottles until the issues are resolved] and 2) microbiology consultation reviewing microbial testing and preservative effectiveness studies).

### 3.2 Animal Pharmacology/Toxicology

Pharmacology/toxicology data for levocetirizine is referenced for the most part for cetirizine the racemic mixture. Refer to section 3.2 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) for further details.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The primary basis for approval of NDA 22-157 and the source of clinical data for this review is the clinical pharmacology BE study A00318, conducted by the applicant. This is a Phase 1 randomized, open-label, crossover, single-dose BE study of LCTZ 5 mg oral tablet and LCTZ 10 mL oral solution (0.5 mg/mL) in 24 healthy, fasting, male and female adults.

### 4.2 Tables of Clinical Studies

Refer to section 4.2 of the clinical review of NDA 22-064 for the table of clinical studies supporting the efficacy and safety of LCTZ 5 mg tablets that formed most of the basis for approval, from a clinical standpoint, of LCTZ for SAR, PAR, and CIU.

### 4.3 Review Strategy

Notwithstanding referencing the approved NDA 22-064 for clinical findings of safety and efficacy supporting LCTZ use in SAR, PAR, and CIU, the review strategy for this NDA is weighted towards the CMC and Clinical Pharmacology review disciplines given that the the development program is based on a single BE study and the applicant is not seeking a new indication or age group.

### 4.4 Data Quality and Integrity

The review does not find any significant data quality or integrity issues; no DSI audit is requested.

### 4.5 Compliance with Good Clinical Practices

The title page of study A00318 states that the trial was conducted in accordance with the ICH E6 Note for Guidance on Good Clinical Practice.

### 4.6 Financial Disclosures

UCB certifies on FDA Form 3454 that it does not enter into any financial arrangement with the clinical investigators that could affect study outcome as defined in 21 CFR 54.2(a), that clinical investigators required to disclose a proprietary interest in the product deny such interests, and that no investigator is the recipient of significant payment of other sorts.

## 5 CLINICAL PHARMACOLOGY

Dr. Partha Roy conducted the clinical pharmacology review of NDA 22-157 (and NDA 22-064) and, from a clinical pharmacology standpoint, recommends approval for the application.

### 5.1 Pharmacokinetics

The pharmacokinetic data most pertinent for this NDA submission are from the applicant's BE study A00318, a comparison of the PK profiles of LCTZ 0.5 mg/mL oral solution and LCTZ 5 mg oral tablet. The results of that clinical pharmacology study form the primary clinical basis for approval of NDA 22-157.

Study A00318 is a randomized, open-label, 2-way crossover, single dose BE study of LCTZ oral solution and tablet in 24 healthy subjects which satisfactorily demonstrates the PK comparability of the two formulations. Two groups of 12 healthy adult male and female subjects received a single dose of either 10 mL of LCTZ 0.5 mg/mL oral solution or 5 mg LCTZ oral tablet under fasting conditions. A minimum 7-day washout period occurred prior to crossover. The 90% confidence intervals for the test to reference ratio calculated for the primary PK parameters (AUC [0-t], AUC, and $C_{max}$) are fully included within the 80% to 125% bioequivalence limits, thereby demonstrating bioequivalence of the oral solution to the oral tablet. The time to $C_{max}$ was reached more rapidly after administration of the oral solution than the tablet (0.50h and 0.67h, respectively). Other PK parameters were consistently comparable between the two formulations. Figure 1 compares mean plasma concentration-time profiles of the 2 formulations and Table 1 summarizes key findings from the study.

**Figure 1. Mean plasma concentration-time profiles of LCTZ formulations**

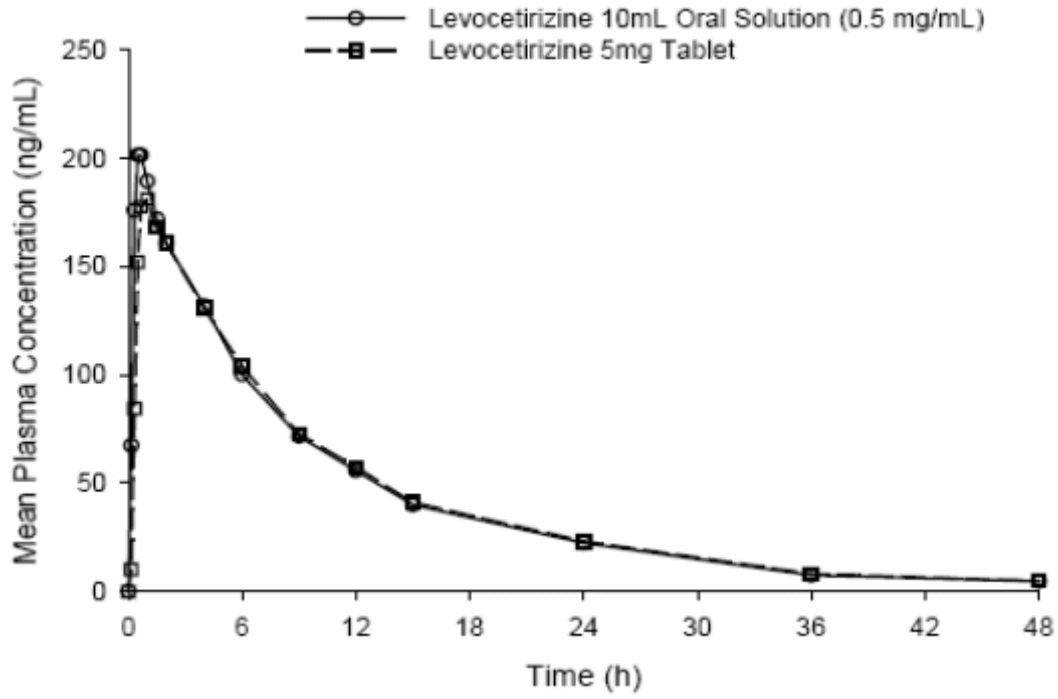


**Table 1. Summary of LCTZ oral tablet and oral solution PK comparisons (Study A00318)**

| Parameter | Reference: LCTZ oral tablet[(a)] | Test: LCTZ oral solution[(a)] | CV[(b)] (%) | Test/Reference ratio | |
|---|---|---|---|---|---|
| | | | | Point estimate | 90% CI |
| AUC (0-t) (ng.h/mL) | 1944 ± 484<br>1887 (1723-2066) | 1954 ± 556<br>1884 (1721-2063) | 7.7 | 99.9 | 96 – 104 |
| AUC (ng h/mL) | 2044 ± 513<br>1943 (1771-2131) | 2020 ± 593<br>1944 (1771-2132) | 7.3 | 100.0 | 96 – 104 |
| $C_{max}$ (ng/mL) | 208 ± 40<br>204 (190-219) | 227 ± 49<br>223 (207-239) | 13.4 | 109.1 | 102 – 117 |
| $t_{max}$ (h) | 0.67 (0.50-4.00) | 0.50 (0.33-2.00) | | -0.30 | -0.42 - -0.17 |

(a): Values are arithmetic means ± standard deviation (SD) on first line, geometric mean (Exp(mean ± SD, ln data)) on second line. $t_{max}$ values are median (range).
(b): Intra-individual coefficient of variation (CV) (%).

Refer to section 5.1 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) as well as Dr. Partha Roy's Clinical Pharmacology review of NDA 22-064 for additional relevant PK information.

## 5.2 Pharmacodynamics

Refer to section 5.2 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) as well as Dr. Partha Roy's Clinical Pharmacology review of NDA 22-064.

### 5.3 Exposure-Response Relationships

There is no linear PK/PD relationship for levocetirizine. Refer to section 5.3 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) as well as Dr. Partha Roy's Clinical Pharmacology review of NDA 22-064.

## 6 INTEGRATED REVIEW OF EFFICACY

Efficacy studies were not required and were not conducted in this development program. Efficacy is supported based on establishment of bioequivalence and reference to efficacy studies conducted with the oral tablet submitted in NDA 22-064. Efficacy studies conducted in adults and adolescents 12 years of age and older confirm that levocetirizine 5 mg tablet is effective for the symptoms of SAR, PAR, and CIU. Efficacy for pediatric patients under 12 years of age is extrapolated from the adult and adolescent data for SAR and PAR, and from the adult data (patients 18 years of age and older) for CIU. Refer to section 6 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) for further details.

### 6.1 Indication

The relief of symptoms associated with seasonal and perennial allergic rhinitis and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The safety data in the bioequivalence study comes for 24 subjects who each received a total of 2 doses of 5 mg levocetirizine dihydrochloride. There were not serious adverse events reported. A total of 51 adverse events were reported in the study. None of these were considered severe. The most frequent adverse events reported were somnolence (n = 8 [33.3%]), and (7[29.2%]) following administration of the oral tablet and the oral solution respectively, and headache reported by 6 (25%) of subjects after both the oral tablet and the oral solution. Somnolence and headache are two of the most frequently reported adverse events reported in the clinical development program for levocetirizine dihydrochloride tablets and are described in the label. There was one report each of dry mouth, nasopharyngitis, diarrhea NOS, and syncope following administration of the oral tablet. With the exception of diarrhea, these adverse events are described in the label for levocetirizine oral tablets. There was one report of pharyngitis following administration of the oral solution. One patient (49 year old male athlete) experience elevated CK (up to 23,650 U/L), and elevated liver enzymes following strenuous physical activity (weight lifting). The enzymes were normal with repeat testing and rechallenge with lecovetirizine 5 mg following a 2-week period of avoidance of strenuous physical activity.

These enzyme abnormalites are not likely related to the study medication. There were no deaths or serious adverse events reported in the single dose BE study. For additional safety information on levocetirizine dihydrochloride refer to NDA 22-064.

# 8 ADDITIONAL CLINICAL ISSUES

As the reason for this NDA submission for LCTZ is a new formulation (oral solution) of an approved product (the oral tablet) proposed for use in the same population and for the same indications as the LCTZ tablet, there are no new or additional clinical issues addressed in this review with the exception of the clinical pharmacology BE study of the 2 product formulations that forms the basis of approval of NDA 22-157.

## 8.1 Dosing Regimen and Administration

The dosing of levocetirizine dihydrochloride oral solution is 2.5 mg (5 mL) once daily in the evening for children 6 to 11 years of age and 5 mg (10 mL) once daily in the evening for adults and adolescents 12 years of age and older. Some adult and adolescent patients may be adequately controlled with 2.5 mg (5 mL)

## 8.2 Drug-Drug Interactions

Refer to section 8.2 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet).

## 8.3 Special Populations

Refer to section 8.3 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet).

## 8.4 Pediatrics

(b) (4)

A consult to Pediatrics regarding the Applicant's potential PREA-related obligations is pending at the time of completion of this clinical review.

## 8.5 Advisory Committee Meeting

The clinical review does not identify issues that warrant advisory committee action.

### 8.6 Literature Review

A literature review was not conducted for this NDA. Refer to list of references following section 10 in the clinical review of NDA 22-064 (LCTZ 5 mg tablet)

### 8.7 Postmarketing Risk Management Plan

The clinical review does not identify concerns that warrant a postmarketing risk management plan.

### 8.8 Other Relevant Materials

None

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

Levocetirizine 0.5 mg/mL oral solution taken as a 2.5 mg or 5 mg dose once daily in the evening is safe and effective for the treatment of symptoms of seasonal, perennial allergic rhinitis, and chronic idiopathic urticaria in patients 6 years of age and older. The bases for this conclusion are the findings of safety and efficacy for the same indications and patient populations of the approved LCTZ 5 mg oral tablet contained in NDA 22-064 and the finding of bioequivalence between the oral solution and oral tablet LCTZ formulations.

Refer to section 9.1 of the clinical review of NDA 22-064 (LCTZ 5 mg tablet) for additional discussion of specific efficacy and safety findings demonstrated in the LCTZ oral tablet clinical development program.

The primary basis for approval of the LCTZ oral solution formulation is the applicant's BE study A00318 which satisfactorily demonstrates comparable BE between the oral solution and oral tablet formulations of LCTZ in 24 healthy male and female adults. The study results show that 10 mL of the LCTZ 0.5 mg/mL solution has a PK profile similar to that of the LCTZ 5 mg tablet based on the extent and rate of absorption assessed by the primary parameters $AUC_{(0-t)}$, AUC, and $C_{max}$.

### 9.2 Recommendation on Regulatory Action

The recommended regulatory action from a clinical standpoint for Levocetirizine 0.5 mg/mL oral solution is for approval at a dose of 2.5 mg or 5 mg once daily in the evening for the relief of symptoms of SAR, PAR, and the treatment of the uncomplicated skin manifestations of CIU in patients 6 years and older.

## 9.3 Recommendation on Postmarketing Actions

The clinical review does not identify a need for specific risk management activities or Phase 4 studies.

### 9.3.1 Risk Management Activity

Refer to section 9.3.

### 9.3.2 Required Phase 4 Commitments

Refer to section 9.3.

### 9.3.3 Other Phase 4 Requests

Refer to section 9.3.

## 9.4 Labeling Review

Refer to section 10.2 for specific details of the preliminary labeling review.

## 9.5 Comments to Applicant

There are no comments based on the clinical review to be conveyed to the applicant.

# 10 Appendices

## 10.1 Review of Individual Study Reports

Refer to section 10.1 of the clinical review of NDA 22-064 (LCTZ 5 mg oral tablet).

## 10.2 Line-by-Line Labeling Review

The clinical review includes a line-by-line review of the applicant's proposed label for LCTZ oral solution compared with the final, approved label for LCTZ 5 mg tablet (NDA 22-064, May, 2007).

Listed below are the differences (text additions or changes are bulletted) between the approved NDA 22-064 label (May, 2007) and the proposed NDA 22-157 label.

In the *Highlights of Prescribing Information* section:

- **"0.5 mg/mL oral solution"**

Under *Recent Major Changes* –

- "Dosage and Administration (2) 03/2007"
- "Dosage and Administration, Adults & Children 12 Years & Older (2.1) 03/2007"
- "Dosage and Administration, Children 6 to 11 Years (2.2) 03/2007"

Under *Dosage and Administration* –

- "…1 tablet or 2 teaspoons [10 mL] oral solution…"
- "…or 1 teaspoon [5 mL] oral solution…"

Under *Dosage Forms and Strengths* –

- "Immediate release oral solution, 0.5 mg per mL (3)"

In the *Full Prescribing Information section:*

Under section 2 *Dosage and Administration* –

- "XYZAL is available as 0.5 mg/mL oral solution and as 5 mg breakable (scored) tablets, allowing for the administration of 2.5 mg, if needed."
- "The recommended dose of XYZAL is 5 mg (1 tablet or 2 teaspoons [10 mL] oral solution) once daily in the evening. Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening." (2.1)

- "The recommended dose of XYZAL is 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening." (2.2)

Under section 3 *Dosage Forms and Strengths* –

- "XYZAL oral solution is a clear, colorless liquid containing 0.5 mg of levocetirizine dihydrochloride per mL."

Under section 11 *Description* –

- "…and oral solution…"

- "XYZAL 0.5 mg/mL oral solution is formulated as an immediate release, clear, colorless liquid. Inactive ingredients are: sodium acetate trihydrate, glacial acetic acid, maltitol solution, glycerin, methylparaben, propylparaben, saccharin, flavoring (consisting of triacetin, natural & artificial flavors, dl-alpha-tocopherol), purified water."

Under section 12 *Clinical Pharmacology* –

- "A dose of 5 mg (10 mL) of XYZAL oral solution is bioequivalent to a 5 mg dose of XYZAL tablets. Following oral administration of a 5 mg dose of XYZAL oral solution to healthy adult subjects, the mean $C_{max}$ was 227 ng/mL and occurred at approximately 0.5 hour." (Absorption, 12.3)
- "The plasma half-life in adult healthy subjects was about 8 hours after administration of oral tablets and 9 hours after administration of the oral solution…" (Elimination, 12.3)

Under section 16 *How Supplied/Storage and Handling*

- "XYZAL oral solution is a clear, colorless liquid containing 0.5 mg of levocetirizine dihydrochloride per mL."
  "Oral solution in 5 oz glass bottles (NDC 0024-5801-20)"
  (b) (4)

Following section 17 –

**"Manufactured for:**
**UCB, Inc.**
Smyrna, GA 30080
and
**sanofi-aventis U.S. LLC**
Bridgewater, NJ 08807
XYZAL is a registered trademark of UCB S.A.
©2007 UCB, Inc., Smyrna GA 30080. All rights reserved."

10.2.1 Additional Labeling Issues

The word "histamine" is added in 2 locations as follows:

1) In the *Highlights of Prescribing Information,* under *Indications and Usage* –

"XYZAL is a *histamine* $H_1$-receptor antagonist indicated for:"

2) In the *Description* section (11) –

"Levocetirizine dihydrochloride…is an orally active *histamine* $H_1$-receptor antagonist."

The word (b) (4) is deleted (see underlined space) from the following sentence in the *Description* section (11) –

""Levocetirizine dihydrochloride…is an orally active _____ histamine $H_1$-receptor antagonist."

10.2.2 DMETS Labeling Consultation

A DMETS consultation (date of review May 23, 2007) includes the following recommendations:

- DMETS has no objections to the use of the proprietary name "Xyzal." (DMETS considers this decision tentative and notes that a re-review of the name by DMETS about 90 days prior to the expected approval date of the NDA is necessary to rule out objections based upon approvals of other proprietary or established names that may have occurred between May 23, 2007 and the NDA approval date).
- DDMAC finds the proprietary name "Xyzal" acceptable from a promotional perspective.
- DMETS recommends implementation of label and labeling revisions to minimize potential errors with product use. Based upon the DMETS recommendations, the labeling comments on the carton, container, and PI listed immediately below (in italics) were sent to the Applicant.

*A. General comments:*

- *The yellow and blue colored bubble graphic appears next to the proprietary name, is very prominent, and detracts from important information on the label and is not acceptable. See 21 CFR 201.15 (a) (6). Delete the bubble graphic.*

- *Spell out the established name in its entirety (i.e., levocetirizine dihydrochloride) to be consistent with that printed in the package insert labeling.*

- *Ensure that the font size of "levocetirizine dihydrochloride" is at least ½ the font size of "Xyzal".*

- *Change the statement of strength to read "2.5 mg/5 mL (0.5 mg/mL)".*

- *Increase the size of the statement of strength.*

- *Relocate the statement of dosage form (oral solution) so that it is positioned adjacent to or below the established name in a separate statement from the product strength.*

- *Ensure that the established name and dosage form are printed in the same font type, size, and boldness.*

- *Ensure that the "manufactured by" information printed on the carton and container labels corresponds to that printed in the PI.*

*B. This comment pertains to the container label:*

- *Ensure child-resistant closure is in accordance with the Poison Prevention Act if these are unit-of-use bottles for outpatient dispensing.*

**(b) (4)**

# REFERENCES

Refer to the References section of the clinical review of NDA 22-064 (LCTZ 5 mg oral tablet).

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/s/
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Robert M Boucher
10/4/2007 05:31:13 PM
MEDICAL OFFICER

It's really OK to sign this time

Lydia McClain
10/5/2007 06:31:23 AM
MEDICAL OFFICER
I concur

# MEDICAL OFFICER REVIEW

## Division Of Pulmonary and Allergy Drug Products (HFD-570)

| | | | |
|---|---|---|---|
| **APPLICATION:** | NDA # 22-157 | **TRADE NAME:** | Xyzal |
| **APPLICANT/SPONSOR:** | UCB, Inc | **USAN NAME:** | Levocetirizine dihydrochloride 0.5 mg/mL oral solution |
| **MEDICAL OFFICER:** | Robert M. Boucher, MD, MPH | | |
| **TEAM LEADER:** | Lydia Gilbert-McClain, MD | **CATEGORY:** | Antihistamine |
| **DUE DATE:** | May 11, 2007 | **ROUTE:** | oral |

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

| Document Date | CDER Stamp Date | Submission | Comments |
|---|---|---|---|
| March 27, 2007 | March 28, 2007 | NDA 22-157, N-000 | Original NDA for new product formulation (oral solution) |

**RELATED APPLICATIONS**

| Document Date | Application Type | Comments |
|---|---|---|
| July 24, 2006 | NDA 22-064 | Original NDA for levocetirizine dihydrochloride (b) mg tablet for SAR, PAR, and CIU in patients six years of age and older |
| November 28, 2006 | PIND 72,233 | PIND meeting package to discuss UCB 505(b)(2) NDA proposal for levocetirizine pediatric liquid formulations |

**REVIEW SUMMARY:**

This is a filing and planning NDA review for levocetirizine 0.5 mg/mL oral solution, a new product formulation, indicated for SAR, PAR, and CIU in children and adults 6 years and older. The NDA [filed under 505(b)(2)] references the pending NDA 22-064 (levocetirizine 5 mg tablets) for drug substance, pre-clinical and clinical pharmacology, and clinical data and is based on a BE study (A00318) that compares BE of the oral solution and tablet formulations of levocetirizine.

**OUTSTANDING ISSUES:** None

**RECOMMENDED REGULATORY ACTION**

| | | | | | |
|---|---|---|---|---|---|
| **IND/NEW STUDIES:** | ____ | **SAFE TO PROCEED** | ____ | **CLINICAL HOLD** | |
| **NDA/SUPPLEMENTS:** | X | **FILEABLE** | ____ | **NOT FILEABLE** | |
| | ____ | **APPROVAL** | ____ | **APPROVABLE** | ____ **NOT APPROVABLE** |
| **OTHER ACTION:** | | | | | |

## I. General Information

Levocetirizine dihydrochloride (LCTZ), the R-enantiomer of the racemate cetirizine, is an oral $H_1$ receptor antagonist proposed for use in the symptomatic treatment of SAR, PAR, and CIU in children and adults age 6 years and older. The NDA proposed product, an oral solution of LCTZ 0.5 mg/mL, is a new formulation. The applicant references the pending NDA (22-064) for LCTZ 5 mg oral tablet for drug substance, pre-clinical, clinical pharmacology, and clinical data, and submits a BE study (A00318) comparing the oral solution and tablet formulations in support of this application (b) (4)

The issues discussed at the PIND 72,233 meeting led UCB to submit the current NDA (22-157) for a liquid formulation in the 6 years and older population (the same population for the 5 mg tablet in NDA 22-064). (b) (4)

The levocetirizine development program began in 1992 and the drug is currently marketed (primarily in 5 mg tablet formulation) in over 80 countries. No clinical studies of LCTZ have been conducted in the U.S. No clinical trials with the proposed oral solution in the NDA-described population have been conducted; there is one completed 4-week, open-label study with this formulation in children 2-6 years old.

(b) (4) The indications, route of administration, patient population (discussed above), and recommendations for use of the oral solution are unchanged from those proposed for LCTZ 5 tablet (pending NDA 22-064).

## II. Regulatory and Foreign Marketing History

### A. Regulatory History

Levocetirizine has not been the subject of a U.S. IND application. The applicant's NDA for LCTZ 5 mg oral tablet, submitted under 505 (b)(2), referencing cetirizine, is under review.

### B. Foreign Marketing History

The applicant began clinical development of LCTZ in Europe in 1992 and the product was first registered in the European Union in 2001 via the Mutual Recognition Procedure. Levocetirizine (5mg tablets) for use in adults and children 6 years of age and older for SAR, PAR, and CIU indications is currently approved in over 80 countries. Fourteen countries where LCTZ is approved have a full 4 year period of marketing exposure, and exposure to LCTZ worldwide as of June 2006 is approximately 3.6 million patient years. The applicant states that LCTZ has not been withdrawn in any country for reasons related to safety or effectiveness.

## III. Items Required for Filing and Reviewer Comments

### A. Reviewer Comments

UCB, Inc, of Smyrna, Georgia, a branch of UCB Pharma, a publicly traded biopharmaceutical company based in Brussels, Belgium submits this NDA. The submission is a Common Technical Document (CTD) hybrid provided as NDA items. Module 1 elements (administrative documents) are provided in both paper and electronic format. The electronic part of the application contains 192 files in 58 folders. As the NDA relies primarily on one BE study and the pending NDA 22-064, several elements are not required for filing (refer to section III B., below). The application contains appropriate financial disclosure information.

### B. Necessary Elements (21 CFR 314.50)

**Table 1. Necessary Elements**

| Item | Type | Status | Location (paper/*electronic*) |
|---|---|---|---|
| | Application Form (FDA 356h) | Present | \nonectd\N22157\N_000\2007-03-27 |
| | Formatting for Electronic Filing | | |
| | Format | Present | \nonectd\N22157\N_000\2007-03-27 |
| | Table of Contents / Indexes | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf |
| | Labeling | Present | \nonectd\N22157\N_000\2007-03-27\labeling |
| 1 | Index / Table of Contents | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf |
| 2 | Samples and Labeling | Present | \nonectd\N22157\N_000\2007-03-27\labeling |
| | Proposed Package Insert | Absent | |
| | Proposed Label | Present | \nonectd\N22157\N_000\2007-03-27\labeling |
| | Proposed Medication Guide | N/A | |
| 3 | Summary | Present | \nonectd\N22157\N_000\2007-03-27\summary |

| Item | Type | Status | Location (paper/*electronic*) |
|---|---|---|---|
| | Labeling | Present | \nonectd\N22157\N_000\2007-03-27\summary\annotated.pdf |
| | Marketing History | Absent | |
| | Chemistry, Manufacturing, & Controls (CMC) | Present | \nonectd\N22157\N_000\2007-03-27\summary\ctdtoc.pdf |
| | Nonclinical Pharmacology and Toxicology | Not required | |
| | Human Pharmacokinetics and Bioavailability | Present | \nonectd\N22157\N_000\2007-03-27\summary\clin-over.pdf |
| | Clinical | Present | \nonectd\N22157\N_000\2007-03-27\summary\clin-sum.pdf |
| | Benefits vs Risks | Absent | \nonectd\N22157\N_000\2007-03-27\summary\clin-over.pdf |
| 4 | CMC | | |
| | Environmental Impact statement | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\othertoc.pdf\cmc\environ.pdf |
| 5 | Nonclinical Pharmacology and Toxicology | Not required | |
| 6 | Human Pharmacokinetics and Bioavailability | Present | \nonectd\N22157\N_000\2007-03-27 |
| 8 | Clinical | Present | \nonectd\N22157\N_000\2007-03-27\clinstat |
| 8.5 | Controlled studies | Not required | |
| 8.7 | Uncontrolled studies | Not required | |
| 8.8 | Integrated Summary of Effectiveness (subsets for age, gender, and race) | Not required | |
| 8.9 | Integrated Summary of Safety | Not required | |
| | Potential for Abuse | N/A | |
| 8.11 | Benefits vs Risks | Present | \nonectd\N22157\N_000\2007-03-27\summary\clin-over.pdf |
| 8.12 | Statements of Good Clinical Practice: | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\hpbio\hpbiotoc.pdf |
| | Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\hpbio\hpbiotoc.pdf |
| | Auditing information | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\hpbio\hpbiotoc.pdf |
| 9 | Safety Updates | Not required | |
| 10 | Statistics | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\clinstat\clintoc.pd |

| Item | Type | Status | Location (paper/*electronic*) |
|---|---|---|---|
| | | | f |
| 11 | Case Report Tabulations | Not required | |
| 12 | Case Report Forms (for patients who died or did not complete studies) | Not required | |
| 13 | Patent Information | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\patinfo.pdf |
| 14 | Patent Certification | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\patcert.pdf |
| 16 | Investigator Debarment Certification | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\debar.pdf |
| 17 | Field copy certification (if applicable) | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\fieldcer.pdf |
| 18 | User Fee Cover Sheet | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\userfee.pdf |
| 19 | Financial Disclosure | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\financial.pdf |
| 20 | Other | | |
| | Claimed Marketing Exclusivity | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\exclusivity.pdf |
| | Pediatric Use | Present | \nonectd\N22157\N_000\2007-03-27\ndatoc.pdf\other\pedsdeferral.pdf |

### C. Decision

This application is fileable.

## IV. Clinical Studies

Support for the NDA is based on a BE study of LCTZ 0.5 mg/mL oral solution and 5 mg tablet in 24 healthy adult male and female subjects (A00318) and reference to pending NDA 22-064 (for LCTZ 5 mg tablet). No clinical trials of the NDA-proposed solution formulation in the intended population have been conducted by the applicant (Module 2, Section 2.5, p 2).

### Bioequivalence Study A00318 Summary

A00318 is a randomized, open-label, crossover, single-dose BE study of LCTZ 5 mg tablet and LCTZ 10 mL oral solution (0.5 mg/mL) in 24 healthy, fasting adult males and females conducted in Belgium in 2002.

Study objectives:

1) BE of the two LCTZ formulations after single-dose administration (plasma AUC and $C_{max}$)

2) Safety → AE's, VS, PE, 12-lead ECG, and laboratory data (CBC, chemistry with liver enzyme profile)

Study design:

There were two 48-hour treatment periods separated by a 7-day washout period. Identical procedures were followed for each treatment period as follows: on Day 1 each subject received (under fasting conditions) a single dose of either 10 mL LCTZ 0.5 mg/mL oral solution or LCTZ 5 mg oral tablet; plasma samples were collected before and at specified times up to 48 hours after drug administration for PK profile determination.

Study results:

1) Both formulations have similar PK profiles (refer to Figure 1 and Table 2)

2) For safety parameters, there were no SAE's. The most frequent AE's were somnolence (reported by 8 [33%] after oral tablet and 7 [29%] after oral solution) and headache (reported by 25% in each group).

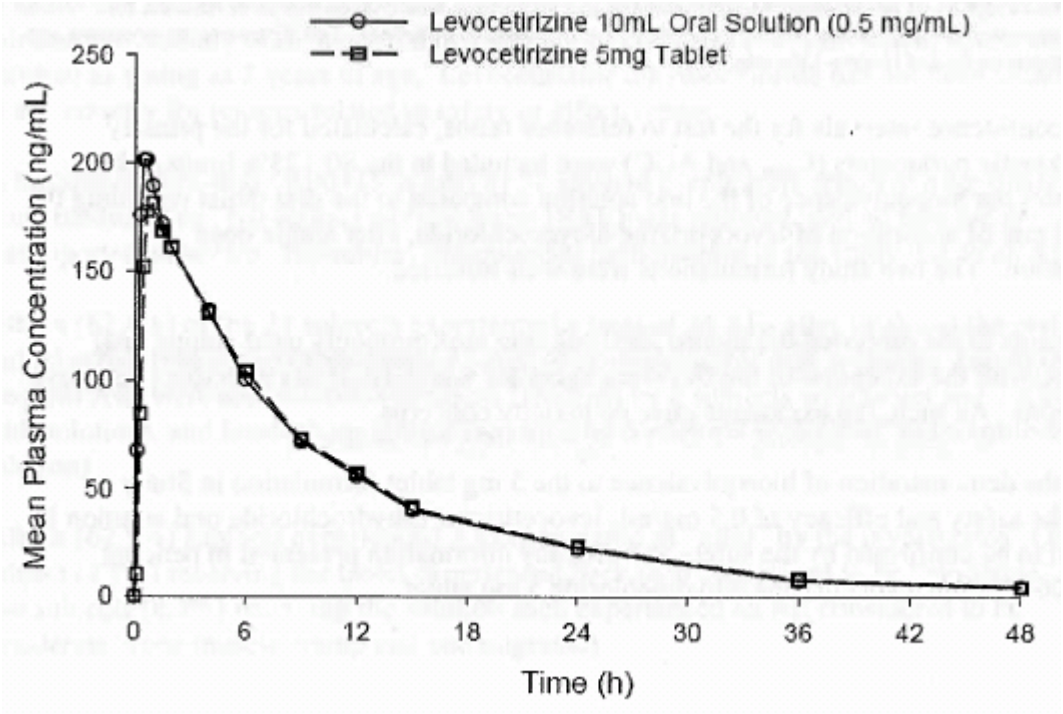
Study conclusions:

1) The primary PK parameters (AUC[0-t], AUC and $C_{max}$) indicate the two formulations are bioequivalent on the basis of extent and rate of LCTZ absorption.

2) Both formulations are safe, and the safety profile is similar for each

(Source: Module 5, Section 3.1.2.1, pp 1-5)

**Figure 1. LCTZ 5 mg single-dose oral tablet and oral solution plasma PK profiles**



(Source: Module 2, Section 2.5, p 3)

**Table 2. LCTZ 5 mg single-dose oral tablet and oral solution plasma PK profiles**

| Parameter | Reference: LCTZ 5 mg tablet | Test: LCTZ oral solution | Test/Reference ratio | |
|---|---|---|---|---|
| | | | Point estimate | 90% CI |
| AUC (0-t) (ng h/mL) | 1944 +/- 484<br>1887 (1723-2066) | 1954 +/- 556<br>1884 (1721-2063) | 99.9 | 96-104 |
| AUC (ng h/mL) | 2004 +/- 513<br>1943 (1771-2131) | 2020 +/- 593<br>1944 (1771-2132) | 100.0 | 96-104 |
| Cmax (ng/mL) | 208 +/- 40<br>204 (190-219) | 227 +/- 49<br>226 (207-239) | 109 | 102-117 |
| Tmax (h) | 0.67 (0.5-4.00) | 0.5 (0.33-2.00) | -0.30 | -0.42 to -0.17 |

(Source: Module 2, Section 2.5, p 4)

## V. DSI Review / Audit

This review finds no issue to warrant DSI review or audit at this time.

## VI. Timeline for Review

**Table 2. Timeline for Review**

| Milestone | Target Date for Completion |
|---|---|
| Stamp Date | March 28, 2007 |
| Study | |
| Draft Review | |
| Label Review | |
| Wrap-up Meeting | November 28, 2007 |
| Due Date | December 12, 2007 |
| PDUFA Date | January 28, 2008 |

## VII. Comments to Applicant

No comments to the applicant are necessary at this time.

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/s/
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Robert M Boucher
5/9/2007 03:50:50 PM
MEDICAL OFFICER

Lydia McClain
5/10/2007 05:22:45 PM
MEDICAL OFFICER
I concur