CLINICAL PHARMACOLOGY REVIEW

NDA:	22-157
Type:	505(b)(2)
Generic Name:	Levocetirizine dihydrochloride
Indication:	Seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children ≥6 yrs.
Dosage Form:	Oral Solution
Strength:	0.5 mg/mL
Route of Administration:	Oral
Dosing regimen:	Once daily
Applicant:	UCB Inc.
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	March 27, 2007
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Wei Qiu, Ph. D.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-157's Clinical Pharmacology information submitted on March 27, 2007 and finds it acceptable provided that a satisfactory agreement is reached between the applicant and the Agency regarding the proposed new language to be included in the package insert.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Levocetirizine dihydrochloride, the active component of Xyzal®, is an orally active H_1-receptor antagonist. The sponsor submitted NDA 22-157, to seek approval of an oral solution of 0.5 mg/mL levocetirizine dihydrochloride in order to provide a liquid dosage formulation alternative to the levocetirizine dihydrochloride 5 mg scored tablet, which is the dosage form recently approved in the Xyzal® NDA 22-064, intended for the treatment of symptoms associated with allergic rhinitis conditions, such as seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU). Levocetirizine is the R-enantiomer of the racemate cetirizine (Zyrtec®).

There are no clinical safety and/or efficacy studies supporting this NDA. One pivotal single-dose bioequivalence study (study A00318) comparing levocetirizine dihydrochloride 5 mg (10 mL of 0.5 mg/mL oral) solution and the 5 mg tablet in healthy subjects is the basis for this NDA.

The bioequivalence of 10 mL of the 0.5 mg/mL (5 mg) levocetirizine dihydrochloride oral solution formulation (Test, Batch no. 11435) with the 5-mg levocetirizine dihydrochloride oral tablet (Reference, Batch no. 12044), has been demonstrated. The two formulations were compared in a two-way crossover design, after single dose administration under fasting conditions; each period was separated by a 7-day washout. Twenty-four subjects (12 males, 12 females) each received two formulations of levocetirizine dihydrochloride 7 days apart.

Mean C_{max} and AUC were similar between the two formulations having geometric mean ratios of test/reference of 1.09 and 1.00, respectively. As shown in Table 1 below, the 90% confidence intervals for the geometric mean ratios, calculated for these two parameters, were fully included in the 0.80-1.25 bioequivalence limits (1.02-1.17 for C_{max} and 0.96-1.04 for AUC), which demonstrates the bioequivalence of the oral solution compared to the oral tablet based on the extent and rate of absorption of levocetirizine dihydrochloride after single dose administration. As expected, peak plasma concentration of the drug following the oral solution administration was slightly earlier than with the tablet (0.50 hours vs. 0.67 hours).

Table 1. Pharmacokinetic parameters and bioequivalence statistics of levocetirizine following single dose administration of a 5 mg tablet and oral solution in healthy subjects.

PK parameters	**Reference: 5 mg tablet**	**Test: 5 mg oral solution**	**Test : Reference ratio**	
			Point estimate	**90% Confidence Intervals**
C_{max} [a] (ng/mL)	208 ± 40 204	227 ± 49 226	1.09	1.02 – 1.17
AUC_{0-t} [a] (ng.hr/mL)	1944 ± 484 1887	1954 ± 556 1884	0.99	0.96 – 1.04
$AUC_{0-\infty}$ [a] (ng.hr/mL)	2004 ± 513 1943	2020 ± 593 1944	1.00	0.96 – 1.04
T_{max} (hr) [b]	0.67 (0.50-4.00)	0.50 (0.33-2.00)		

[a] 1st line: arithmetic mean ± SD; 2nd line: geometric mean
[b] median (range)

Reviewer:
Partha Roy, Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 2

Concurrence:
Wei Qiu, Ph.D., Team leader (Acting)

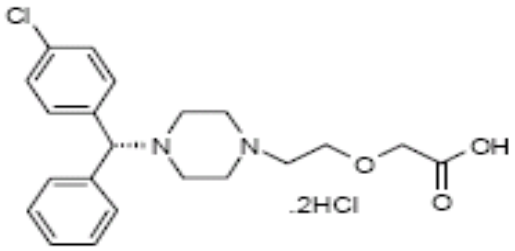
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the general attributes of Levocetirizine dihydrochloride?

Levocetirizine dihydrochloride has one chiral center and is the R enantiomer (ucb 28556) of the racemate cetirizine hydrochloride. Cetirizine hydrochloride is registered in the US as Zyrtec®. Levocetirizine dihydrochloride drug product is recently approved for marketing under the trade name Xyzal®, an immediate-release, white to off-white, oval film-coated scored oral tablet containing 5 mg of levocetirizine dihydrochloride. [redacted] Levocetirizine is believed to be the sole active enantiomer in cetirizine. The chemical name of levocetirizine dihydrochloride is (R)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1- piperazinyl]-ethoxy] acetic acid hydrochloride. The chemical structure of levocetirizine dihydrochloride is provided below.

STRUCTURAL FORMULA:



Molecular formula: $C_{21}H_{25}N_2O_3Cl.2HCl$
Molecular weight: 461.8
Solubility: Levocetirizine dihydrochloride is a white to off white powder. It is freely soluble in water [redacted]
Octanol-Water Partition Coefficient: At pH 7.4 is 1.32 ± 0.03.
Hygroscopicity: Not hygroscopic
Melting Range: about 215 – 220 °C

FORMULATION
Levocetirizine dihydrochloride 0.5 mg/mL, supplied for oral use as a solution with water vehicle was developed to provide an additional dosage form option.

INDICATION (as per proposed label)
Xyzal® (levocetirizine dihydrochloride) is indicated for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), and for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 years of age or older.

DOSAGE AND ADMINISTRATION (as per proposed label)

XYZAL tablets are white, film-coated, oval-shaped, scored, imprinted (with the letter Y in red color on both halves of the scored tablet) and contain 5 mg levocetirizine dihydrochloride.

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

Adults and Children 12 Years of Age and Older: 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.

Children 6 to 11 Years of Age: The recommended dose of XYZAL is 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening. The 2.5 mg dose should not be exceeded because the systemic exposure with 5 mg is approximately twice that of adults

The drug product can be taken without regard to food.

2.2 General Clinical Pharmacology

2.2.1 What is known about the pharmacokinetics of Xyzal® solution?

The sponsor evaluated single-dose pharmacokinetics of levocetirizine under fasted conditions in an open-label, randomized, cross-over bioequivalence study of levocetirizine dihydrochloride 5 mg tablet and levocetirizine dihydrochloride 10 mL oral solution (0.5 mg/mL) in 24 healthy subjects, the results of which are presented below in Table 2. Levocetirizine was found to be rapidly absorbed with a median T_{max} of 0.5 hrs following single dose administration.

Table 2. Mean (SD) pharmacokinetic parameters of levocetirizine following 5 mg (10 mL of 0.5 mg/mL) administration of Xyzal® oral solution

PK parameters	Oral Solution (0.5 mg/mL)
AUC_{0-t} (ng.hr/mL)	1954 ± 556
AUC_{0-inf} (ng.hr/mL)	2020 ± 593
C_{max} (ng/mL)	227 ± 49
T_{max} (hr)	0.5 (0.33 – 2.00)*
$T_{1/2}$ (hr)	9 ± 3.1
V_d/F (L)	34 ± 14
CL/F (mL/min)	44 ± 12

* median (range)

2.3 General Biopharmaceutics

2.3.1 What is the solubility and permeability of the drug substance?

Levocetirizine is a highly soluble (94.6 g/100 mL) and a moderately permeable (approximately 86% of radioactivity excreted in urine in a mass balance study) drug. The permeability of levocetirizine (P_{app}: 4.38×10^{-6} cm/s) was determined to be intermediate.

2.3.2 What was the relative bioavailability of the new oral solution form when compared to the currently marketed tablet dosage form of Xyzal®? Was bioequivalence demonstrated between the two formulations?

Yes. The bioequivalence of 10 mL of the 0.5 mg/mL (5 mg) levocetirizine dihydrochloride oral solution formulation (Test, Batch no. 11435, 200 mL bottle) with the 5-mg levocetirizine dihydrochloride oral tablet (Reference, Batch no. 12044), has been demonstrated under fasted conditions in study A00318 as evidenced by the observation that the 90% CIs for the ratios of the geometric means for C_{max} and AUC were within the goal post for bioequivalence (80-125%) for levocetirizine (Table 3).

Study A00318 was a prospective, open-label, single dose, 2-way crossover study in 24 healthy subjects (12 males and 12 females) conducted to determine the relative bioavailability of the proposed oral solution formulation of Xyzal® compared to that of the currently marketed reference formulation of Xyzal® tablet. The subjects were randomized and placed into one of two treatment groups under fasted state: 1) Treatment A (test): 10 mL of 0.5 mg/mL oral solution; Treatment B (reference): 5 mg oral tablet. There was a minimum of 7-day washout between doses.

Plasma levocetirizine concentration-time profiles following administration of the treatments are shown in Figure 1.The mean PK parameters and statistical analysis of levocetirizine for the two formulations are summarized in Table 3.

Figure 1: Mean plasma concentration-time profiles of levocetirizine

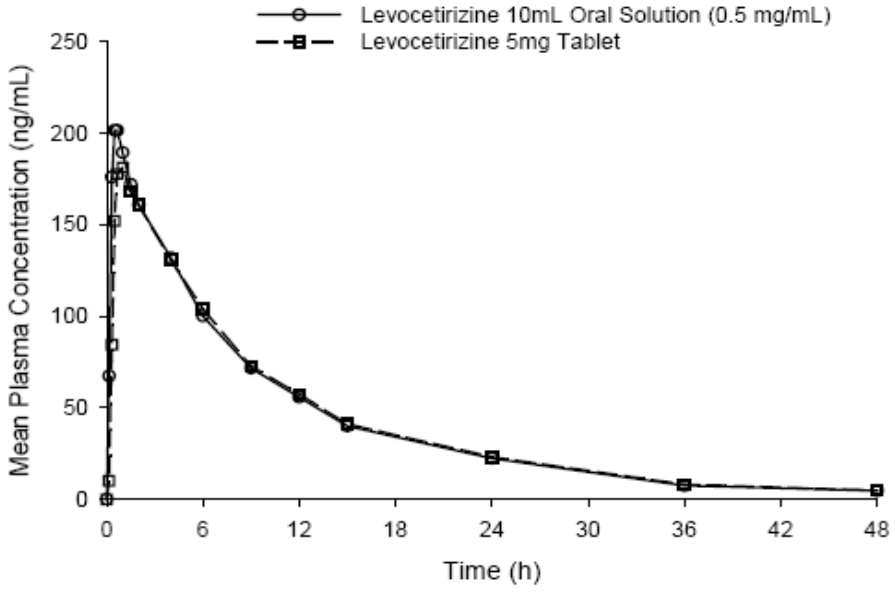


Table 3. Pharmacokinetic parameters of levocetirizine along with point estimates and 90% confidence intervals following single dose administration of a 5 mg oral tablet and 5 mg oral solution in healthy subjects.

Parameter	Reference: Levocetirizine oral tablet[a]	Test: Levocetirizine oral solution[a]	CV[b] (%)	Test/Reference ratio[c]	
				Point estimate	90% CI
AUC(0-t) (ng.h/mL)	1944 ± 484 1887 (1723 – 2066)	1954 ± 556 1884 (1721 – 2063)	7.7	99.9	96 – 104
AUC (ng.h/mL)	2004 ± 513 1943 (1771 – 2131)	2020 ± 593 1944 (1771 – 2132)	7.3	100.0	96 – 104
C_{max} (ng/mL)	208 ± 40 204 (190 – 219)	227 ± 49 226 (207 – 239)	13.4	109	102 – 117
t_{max} (h)	0.67 (0.50 – 4.00)	0.50 (0.33 – 2.00)		-0.30	-0.42 to -0.17
λ_z (h^{-1})	0.085 ± 0.017	0.083 ± 0.021			
$t_{1/2}$ (h)	8.4 ± 1.7	9.0 ± 3.1			
MRT (h)	11.5 ± 2.5	11.4 ± 2.6			
V_z/f (L)	31 ± 4	34 ± 14			
V_z/f (L/kg)	0.44 ± 0.08	0.47 ± 0.15			
CL/f (mL/min)	44 ± 11	44 ± 12			
CL/f (mL/min/kg)	0.63 ± 0.21	0.63 ± 0.21			

[a]: Values are arithmetic means ± SD on first line, geometric mean (Exp(mean±SD, ln data)) on second line. t_{max} values are median (range).
[b]: Intra-individual CV (%).
[c]: Point estimate and 90% CI for the expected Test/Reference geometric mean ratio (%), derived from ANOVA for continuous parameters; for t_{max}, median estimator and 90% CI of the expected difference. Test-Reference (h) calculated with the non-parametric method of Hodges-Lehmann.

The $AUC_{0-\infty}$ and the AUC_{0-t} were similar between the two formulations. The geometric means ratios were fully included within the 80-125% bioequivalence range. Similarly, 90% CI of the geometric mean ratio for C_{max} remained within the bioequivalence range of 80-125%. The peak plasma concentration of the drug following the oral solution administration was slightly earlier than with the tablet (0.50 hours vs. 0.67 hours).

2.3.3 Did the sponsor use to-be-marketed formulation in the pivotal bioequivalence trial?

Yes. The formulation proposed for registration is the same as that used in the pivotal bioequivalence trial (study A00318).

2.3.4 What is the composition of the to-be-marketed formulation?

All inactive ingredients used in the manufacture of Xyzal® 0.5 mg/mL oral solution meet compendial requirements, except for the tutti frutti flavor for which the applicant has developed in-house specifications. Table 4 lists the compendial inactive ingredients.

Table 4. Compendial inactive ingredients in Xyzal® oral solution

Components	Function	Reference
Sodium acetate trihydrate		Current USP
Glacial acetic acid		Current USP
Maltitol Solution		Current NF
Glycerin		Current USP
Methylparaben		Current NF
Propylparaben		Current NF
Saccharin sodium		Current USP
Tutti frutti flavor 501103A7		UCB Specification
Purified water		Current USP

2.4 Analytical Section

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

Levocetirizine has been measured in plasma by using an achiral validated method utilizing liquid chromatography with tandem mass spectrometric detection. According to this reviewer, although some chiral interconversion may happen, there is no evidence to suggest any substantial chiral interconversion taking place *in vivo*. Therefore, the use of the achiral chromatographic method in the pivotal bioequivalence study (A00318) of levocetirizine dihydrochloride oral solution is justified.

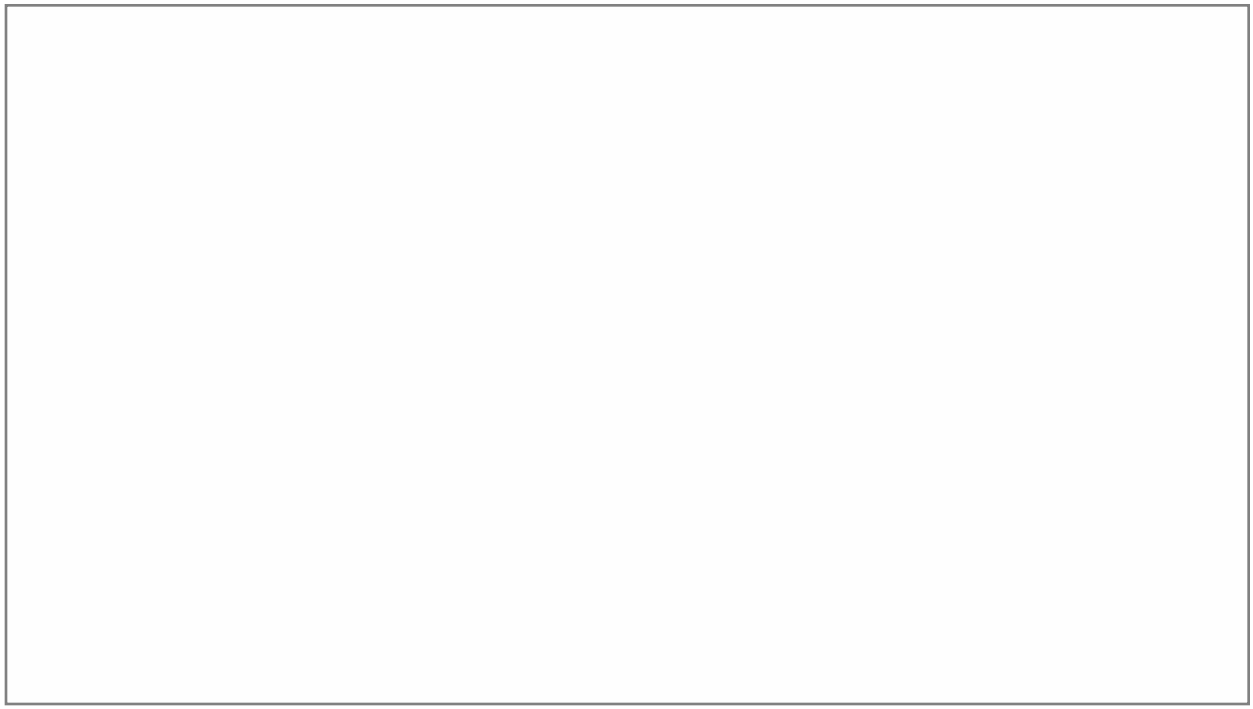
The analytical method achieved chromatographic separation after liquid-liquid extraction on a

Interday precision and accuracy of the method were evaluated using the results of the quality control samples (QCS) assayed daily alongside the clinical samples. Table 5 summarizes the findings from the in-study validation of the method.

Table 5. Assay performance (in-study validation) for levocetirizine

	Levocetirizine
Linearity	Satisfactory: Standard curve ranged from 2 to 500 ng/mL: $r^2 > 0.999$
Accuracy	Satisfactory: % Bias: -6.02 at 4 ng/ml; -2.03 at 40 ng/mL; -0.667 at 400 ng/mL
Inter-day Precision	Satisfactory: % CV: 6.74 at 4 ng/ml; 3.99 at 40 ng/mL; 4.53 at 400 ng/mL
Specificity	Satisfactory: sample chromatograms submitted

3 DETAILED LABELING RECOMMENDATIONS



4. APPENDICES
4.1 PROPOSED PACKAGE INSERT

Pages 11 through 23 redacted for the following reasons:
- -

4.2. OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-157**	**Brand Name**	**Xyzal®**
OCP Division	**DCP2**	**Generic Name**	**Levocetrizine dihydrochloride**
Medical Division	**DPAP**	**Drug Class**	**Oral H_1-histamine receptor antagonist**
OCP Reviewer	**Partha Roy**	**Indication(s)**	**Symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), & chronic idiopathic urticaria (CIU) in adults and children ≥ 6 yrs**
OCP Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Oral solution**
		Dosing Regimen	**0.5 mg/mL**
Date of Submission	**28 Mar 2007**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**31 July 2007**	**Sponsor**	**UCB Inc.**
PDUFA Due Date	**28 Jan 2008**	**Priority Classification**	**Standard**
Division Due Date	**27 Nov 2007**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			**Cetirizine bioanalytical report submitted instead of levocetirizine. See comments to be sent to the sponsor below**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
17 Healthy Volunteers-				
single dose:	x			
multiple dose:				
18 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**1**			
19				

20 Filability and QBR comments

21	**"X" if yes**	**22 Comments**
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		**1. The analytical report submitted with Study A00318 is for the determination of cetirizine dihydrochloride in human plasma. Study A00318 is a bioequivalence study measuring levocetirizine in human plasma. Therefore, provide the correct analytical report, i.e. for Levocetirizine.** **2. Provide individual subject data listings indicating calendar dates of screening, discharge from the clinic, last follow-up visit and dosing (both periods).**
QBR questions (key issues to be considered)		**1. Demonstration of Bioequivalence between levocetirizine 5 mg tablet vs. 0.5 mg/mL oral solution.** **2. Conduct of bioanalytical sample analysis and method validation to support the pivotal BE study**
Other comments or information not included above		
Primary reviewer Signature and Date	**Partha Roy 16 May 2007**	

Secondary reviewer Signature and Date	**Emmanuel Fadiran 16 May 2007**

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

/s/

Partha Roy
10/17/2007 01:29:05 PM
BIOPHARMACEUTICS

Wei Qiu
10/17/2007 01:31:42 PM
BIOPHARMACEUTICS