

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-157

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	January 17, 2008
From	Wei Qiu, Ph.D., Clinical Pharmacology Acting Team Leader
Subject	Cross-Discipline Team Leader Review
NDA	22-157
Proprietary / Established (USAN) names	XYZAL®/Levocetirizine dihydrochloride
Dosage forms / strength	Oral solution/0.5 mg per mL
Proposed Indication(s)	Seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in adults and children \geq 6 yrs
Recommended:	<i>Approval</i>

1. Introduction to Review

UCB, Inc. submitted a 505(b)(2) New Drug Application (NDA 22-157) on March 27, 2007 for an oral solution of 0.5 mg per mL levocetirizine dihydrochloride for the relief of symptoms associated with seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in adults and children 6 years of age and above. The PDUFA due date is January 28, 2008.

This application is supported by the demonstration of bioequivalence (BE) of the proposed oral solution to an approved reference product (Xyzal®, 5 mg scored tablet) and relevant CMC information of the drug product.

The major issue identified during the review cycle was the presence of (b) (4) leachables (b) (4) in the (b) (4) 9 bottles and (b) (4) leachables (b) (4) in the (b) (4) 9 bottles. It was found that the respective exposures of these leachables were (b) (4) μ g threshold and needed to be (b) (4) μ g or be qualified to be acceptable. The sponsor addressed this issue by committing to only dispensing the levocetirizine dihydrochloride oral solution in the 15 mL and 150 mL amber glass bottles and not in the originally proposed (b) (4) bottles until the Agency's concerns are addressed.

There are no other outstanding issues that may impact the approval of this application.

Pending mutual agreement between the agency and sponsor on the labeling language, the recommendation for this NDA is an Approval.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Levocetirizine, the R-enantiomer of the racemate cetirizine (Zyrtec®), is a H1-receptor antagonist. An oral immediate release formulation of levocetirizine (Xyzal® scored tablets) was approved on May 25, 2007 under NDA 22-064. It was approved for the relief of symptoms associated with seasonal and perennial allergic rhinitis and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. The recommended dose is 5 mg (one tablet) once daily in the evening for adults and children 12 years of age and older and 2.5 mg (one half tablet) once daily in the evening for children 6 to 11 years of age.

Xyzal® (levocetirizine 5 mg tablet) 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. The sponsor states that levocetirizine has not been withdrawn in any country for reasons related to safety or effectiveness.

UCB, Inc. submitted NDA 22-157 for levocetirizine 0.5 mg per mL oral solution under section 505(b)(2) referencing NDA 22-064. With the establishment of bioequivalence between the proposed oral solution and approved oral tablet, clinical efficacy and safety data are not required to support approval of the proposed oral solution.

3. CMC/Microbiology/Device

3.1. General product quality considerations

Xyzal® oral solution 0.5 mg/mL provides an alternative dosage form to the recently approved 5 mg oral tablet. The drug substance is levocetirizine dihydrochloride, the R-enantiomer of cetirizine hydrochloride, the active ingredient in the approved Zyrtec® antihistamine products. The (b) (4) is controlled to a level of (b) (4)% or less.

All information for the drug substance is referenced to the related NDA 22-064 for Xyzal® (levocetirizine dihydrochloride) tablets. The same sites were used for drug substance manufacture.

Levocetirizine dihydrochloride is soluble in water. The aqueous-based drug product formulation is (b) (4) to pH of (b) (4) and also includes maltitol solution, glycerin, saccharin (b) (4) methylparaben and propylparaben, and (b) (4) flavoring. The product will be packaged in 5 oz. (148 mL) amber glass bottles for marketing and there will also be 15 mL amber glass bottle for physician samples. The drug product is manufactured at UCB Manufacturing, Inc., Rochester, NY.

The final drug product was used in the BE study.

3.1.1. Facilities review/inspection

The Office of Compliance and New Drug Quality find the facilities for drug substance and drug product manufacturing acceptable (see Dr. Craig M. Bertha's chemistry review).

3.2. Other notable issues (resolved)

During review of this application, the Chemist (see Dr. Craig M. Bertha's chemistry

(b) (4)

An issue with microbial limits, preservative effectiveness testing and preservative assay acceptance criteria was consulted to Microbiology on April 6, 2007. The review is pending at this time.

4. Nonclinical Pharmacology/Toxicology

Preclinical pharmacology and toxicology assessment of levocetirizine is mainly based on prior findings of safety and effectiveness for cetirizine tablets (NDA 19-835). Pharmacology and genotoxicity profiles of levocetirizine were compared to cetirizine in 4- and 13-week bridging toxicity studies in rats and dogs, and embryo-fetal bridging studies in rats and rabbits (NDA 22-064). No new nonclinical pharmacology/toxicology studies were required or conducted for this application. Details of the assessment can be found in the primary and secondary pharmacology/toxicology reviews.

5. Clinical Pharmacology/Biopharmaceutics

Based on the approved labeling for Xyzal® tablets and the bioequivalence study results included in this current submission, the following information is included in the proposed labeling for oral solution and tablets.

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Pharmacokinetics

Levocetirizine exhibited linear pharmacokinetics over the therapeutic dose range in adult healthy subjects.

- Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. Food had no effect on the extent of exposure (AUC) of the levocetirizine tablet, but T_{max} was delayed by about 1.25 hours and C_{max} was decreased by about 36% after administration with a high fat meal; therefore, levocetirizine can be administered with or without food.

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 peak plasma concentrations were achieved approximately 0.5 hour post-dose.

- Distribution

The mean plasma protein binding of levocetirizine *in vitro* ranged from 91 to 92%, independent of concentration in the range of 90-5000 ng/mL, which includes the therapeutic plasma levels observed. Following oral dosing, the average apparent volume of distribution is approximately 0.4 L/kg, representative of distribution in total body water.

5.2. Drug-drug interactions

In vitro data on metabolite interaction indicate that levocetirizine is unlikely to produce, or be subject to metabolic interactions. Levocetirizine at concentrations well above C_{max} level achieved within the therapeutic dose ranges is not an inhibitor of CYP isoenzymes 1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and is not an inducer of UGT1A or CYP isoenzymes 1A2, 2C9 and 3A4.

No formal *in vivo* drug interaction studies have been performed with levocetirizine. Studies have been performed with the racemic cetirizine.

Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole, and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect.

Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.

5.3. Pathway of Elimination

- Metabolism

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of hepatic drug metabolizing enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation, and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involves multiple and/or unidentified CYP isoforms.

- Elimination

The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and oral solution, and the mean oral total body clearance for levocetirizine was approximately 0.63 mL/kg/min. The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Renal clearance of levocetirizine correlates with that of creatinine clearance. In patients with renal impairment the clearance of levocetirizine is reduced.

- Renal Impairment

Levocetirizine exposure (AUC) exhibited 1.8-, 3.2-, 4.3-, and 5.7-fold increase in mild, moderate, severe, renal impaired, and end-stage renal disease patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, 2.9-, and 4-fold, respectively.

The total body clearance of levocetirizine after oral dosing was correlated to the creatinine clearance and was progressively reduced based on severity of renal impairment. Therefore, it is recommended to adjust the dose and dosing intervals of levocetirizine based on creatinine clearance in patients with mild, moderate, or severe renal impairment. In end-stage renal disease patients (CLCR < 10 mL/min) levocetirizine is contraindicated. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was <10%.

The dosage of XYZAL should be reduced in patients with mild renal impairment. Both the dosage and frequency of administration should be reduced in patients with moderate or severe renal impairment.

- Hepatic Impairment

XYZAL has not been studied in patients with hepatic impairment. The non-renal clearance (indicative of hepatic contribution) was found to constitute about 28% of the total body clearance in healthy adult subjects after oral administration.

As levocetirizine is mainly excreted unchanged by the kidney, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment.

5.4. Demographic interactions/special populations

- Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 mL/min/kg) appears to be comparable to that in men (0.59 ± 0.12 mL/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

- Pediatric Patients

Data from a pediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 6 to 11 years with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean C_{max} was 450 ng/mL, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this pediatric population than in adults.

- Geriatric Patients

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the XYZAL dose should be adjusted in accordance with renal function in elderly patients.

- Race

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

5.5. Thorough QT study or other QT assessment

A QT/QTc study using a single dose of 30 mg of levocetirizine did not demonstrate an effect on the QTc interval. While a single dose of levocetirizine had no effect, the effects of levocetirizine may not be at steady state following single dose. The effect of levocetirizine on the QTc interval following multiple dose administration is unknown. Levocetirizine is not expected to have QT/QTc effects because of the results of QTc studies with cetirizine and the long post-marketing history of cetirizine without reports of QT prolongation.

5.6. Other notable issues (resolved)

The clinical pharmacology program consisting of one BE study (Study A00318) addressed the key issue of bioequivalence between the proposed 0.5 mg per mL oral solution and the reference, Xyzal® tablets to support the efficacy and safety of the 0.5 mg per mL oral solution. Detailed review of this study can be found in Dr. Partha Roy's Clinical Pharmacology review dated October 17, 2007.

Study A00318 was a single dose, 2-way crossover study in 24 healthy subjects (12 males and 12 females). The subjects were given 10 mL of 0.5 mg/mL oral solution (Treatment A as the test) and 5 mg oral tablet (Treatment B as the reference) under fasting condition. There was a minimum of 7-day washout period between treatments.

Table 1. Arithmetic mean \pm SD (geometric mean) pharmacokinetic parameters of levocetirizine and statistical analysis

Parameter	Levocetirizine Oral Tablet (Reference)	Levocetirizine Oral Solution (Test)	Geometric Mean Ratio (Test/Reference) (90% CI)
AUC _t (ng.hr/mL)	1944 \pm 484 (1887)	1954 \pm 556 (1884)	0.999 (0.96, 1.04)
AUC _{inf} (ng.hr/mL)	2004 \pm 513 (1943)	2020 \pm 593 (1944)	1.000 (0.96, 1.04)
C _{max} (ng/mL)	208 \pm 40 (204)	227 \pm 49 (226)	1.09 (1.02, 1.17)
T _{max} * (hr)	0.67 (0.50 – 4.00)	0.50 (0.33 – 2.00)	--

*T_{max} values are median (range).

Results (**Table 1**) showed that the 0.5 mg/mL oral solution is bioequivalent to oral tablets since the 90% CI of the geometric mean ratios for AUC_t, AUC_{inf}, and C_{max} fell within the bioequivalence limit of 0.80 to 1.25. The medium T_{max} of oral solution is slightly shorter than oral tablets (0.50 hr vs 0.67 hr).

6. Clinical Microbiology (where relevant; e.g., antimicrobial therapeutics)

This is not relevant to this application.

7. Clinical/Statistical

The efficacy and safety of the oral solution is completely relying on a BE study and the findings from NDA 22-064. No additional clinical studies were required to support this application. The BE study demonstrated that under fasting conditions, the proposed oral solution is BE to the reference tablet. The medical officer reviewed the safety data from the BE study and found no serious adverse events. The most frequent adverse events were somnolence (n = 8 [33.3%]), and (7[29.2%]) following administration of the oral tablet and oral solution respectively, and headache (n = 6 (25%)) after both the oral tablet and the oral solution (see Dr. Robert M. Boucher's clinical review). For additional safety information on levocetirizine dihydrochloride, the readers are referred to NDA 22-064.

Clinical studies in children under 2 years of age with SAR and in children under 6 months of age with PAR or CIU are waived because the disease does not exist or is difficult to diagnose in these age groups. Clinical studies in children 2 to 6 years of age with SAR and children 6 months to 6 years of age with PAR or CIU are deferred. The agency proposed to include this information in the labeling to comply with the Pediatric Research Equity Act of 2007 (PREA).

8. Advisory Committee Meeting

There was no need for an advisory committee meeting for this application.

9. Other Relevant Regulatory Issues

No other relevant regulatory issues were identified at the completion of this CDTL memo.

10. Financial Disclosure

The applicant certifies on FDA Form 3454 that there was no financial arrangement with the clinical investigators that could affect study outcome. The applicant stated that the clinical investigators certified that they did not have proprietary interest and no investigator receive significant payment of other sorts.

11. Labeling

The applicant updated the approved labeling for Xyzal® oral tablets with information of oral solution. The labeling will be for both oral tablet and oral solution.

11.1. Proprietary name

No issues have been identified with regards to proprietary name at the completion of this CDTL memo (see Dr. Loretta Holmes's review dated August 24, 2007).

11.2. Physician labeling

Labeling was reviewed by all disciplines and comments were sent to the sponsor.

11.3 Carton and immediate container labels

No issue was identified from DDMAC consult (Dr. Michelle Safarik's review dated May 3, 2007). DMETS consult recommended that the dosage strength for the oral solution be presented as 2.5 mg/5 mL instead of 0.5 mg/mL on the carton/container labels and in the package insert.

11.4 Patient labeling/Medication guide

No issues have been identified at the completion of this CDTL memo.

12. DSI Audits

DSI inspection was not requested for the bioequivalence study because the oral solution is a simple formulation of an approved product.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

The established bioequivalence of the proposed oral solution to the approved oral tablet under fasting condition support the efficacy as well as safety of levocetirizine 0.5 mg/mL oral solution. Since food had no effect on the extent of exposure as reflected in the approved labeling for oral tablet, oral tablet was recommended to be taken with or without food. For the oral solution formulation, food effect is not expected.

This application is recommended for approval.

13.2. Safety concerns to be followed postmarketing

No safety concern has been identified to be followed postmarketing.

13.3. Risk Minimization Action Plan, if any

There is no need for risk minimization consideration for the oral solution.

13.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)

No postmarketing studies are recommended for oral solution.

13.5. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)

No specific comments need to be conveyed to the applicant.

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

/s/

Chandra Sahajwalla
1/28/2008 12:10:00 PM
BIOPHARMACEUTICS

There were problems with DFS and IT is in
process of resolving the issues. This review/memo written
by Wei Qiu is being sent from Chandra
Sahajwalla's account and she will sign off.

Wei Qiu
1/28/2008 12:11:55 PM
BIOPHARMACEUTICS