CLINICAL REVIEW

Application Type	NDA
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Submission Code	
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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 and maltitol (USP) sodium acetate, glacial acetic acid, and sodium acetate trihydrate methylparaben and propylparaben saccharin sodium Tutti frutti flavor 501103A7; and purified water

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

[redacted]

Therefore, 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 [redacted] and although its current safety database for the pediatric age group less than 6 years of age does not support use in children less than 6 years old, [redacted] includes a request for deferral of data submission [redacted] 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 [redacted] sodium acetate/acetic acid and includes maltilol solution, glycerin, saccharin sodium, tutti frutti flavoring, and [redacted] methyl- and propylparaben. The solution is packaged in 5 ounce [redacted] glass [redacted] bottles and is demonstrated to have adequate stability to support a 24 month shelf life.

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

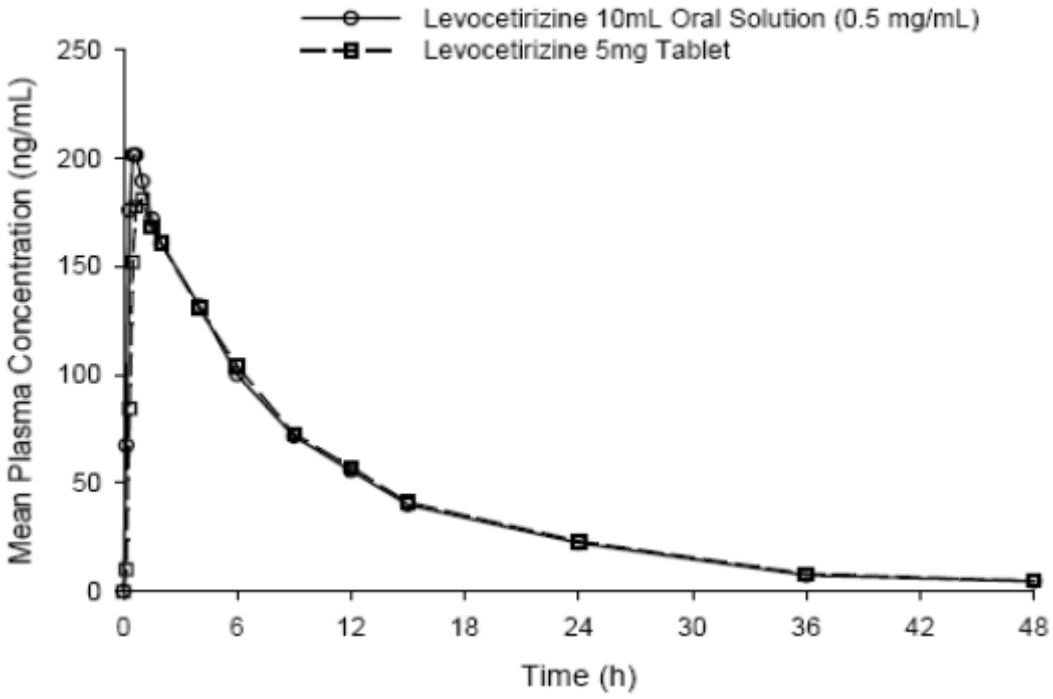


Table 1. Summary of LCTZ oral tablet and oral solution PK comparisons (Study A00318)

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 1887 (1723-2066)	1954 ± 556 1884 (1721-2063)	7.7	99.9	96 – 104
AUC (ng.h/mL)	2044 ± 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 ± 49 223 (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

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

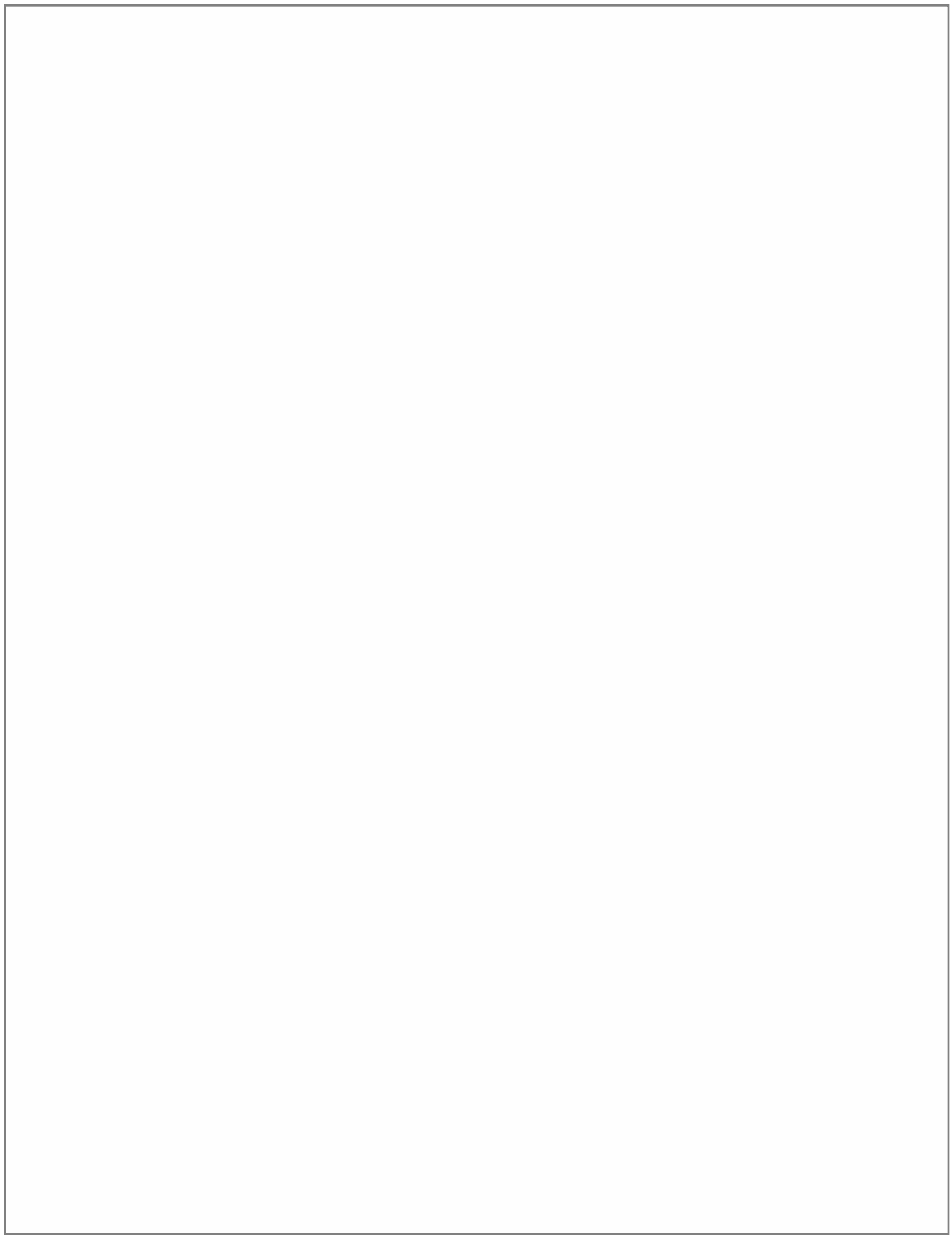
There are no comments based on the clinical review to be conveyed to the applicant.

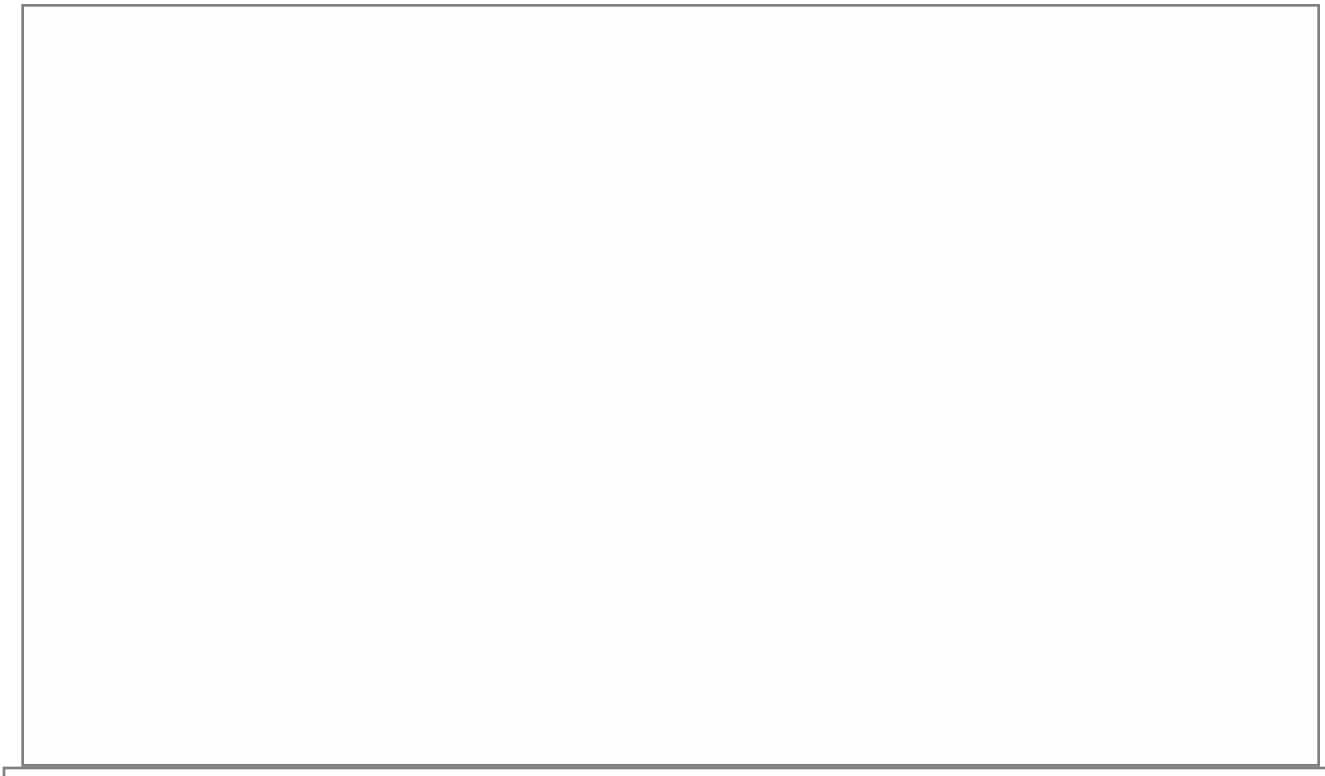
10 Appendices

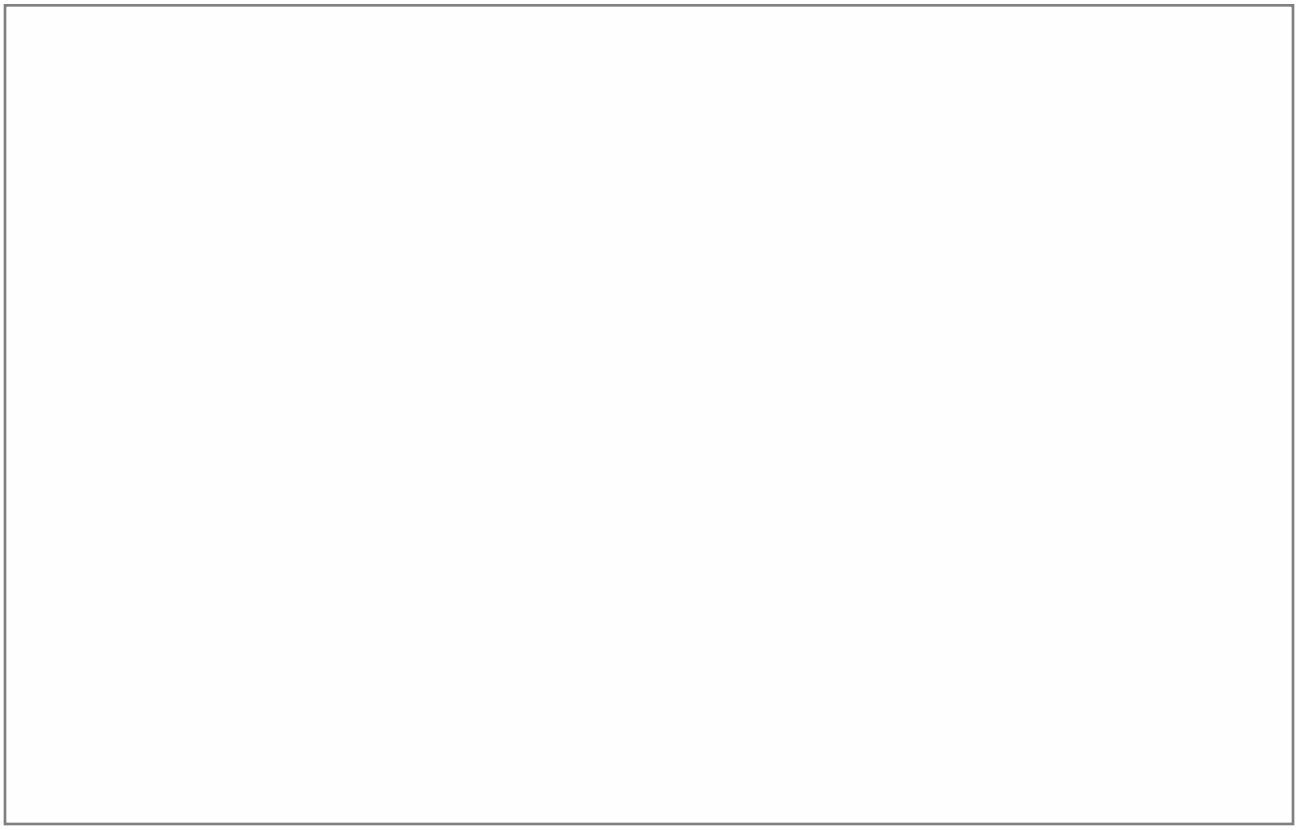
10.1 Review of Individual Study Reports

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







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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10/4/2007 10:13:07 AM
MEDICAL OFFICER

Lydia McClain
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I concur