CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-064

CHEMISTRY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET
CHEMISTRY CONSULT

NDA number: 22-064
Date/type of submission: 1; 7/24/06/original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: UCB, Inc.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: **Division of Pulmonary and Allergy Drug Products**
Review completion date: 2/22/07

Drug:

Trade name: XYZAL
Generic name: levocetirizine
Code name: ucb 28556
Chemical name: 2-{(R)4[(4-chlorophenyl) phenylmethyl]-1-piperazinyl}ethoxy acetic acid dihydrochloride
CAS registry number: 130018-87-0

Drug class: H_1 receptor antagonist

Intended clinical population: Allergic patients.

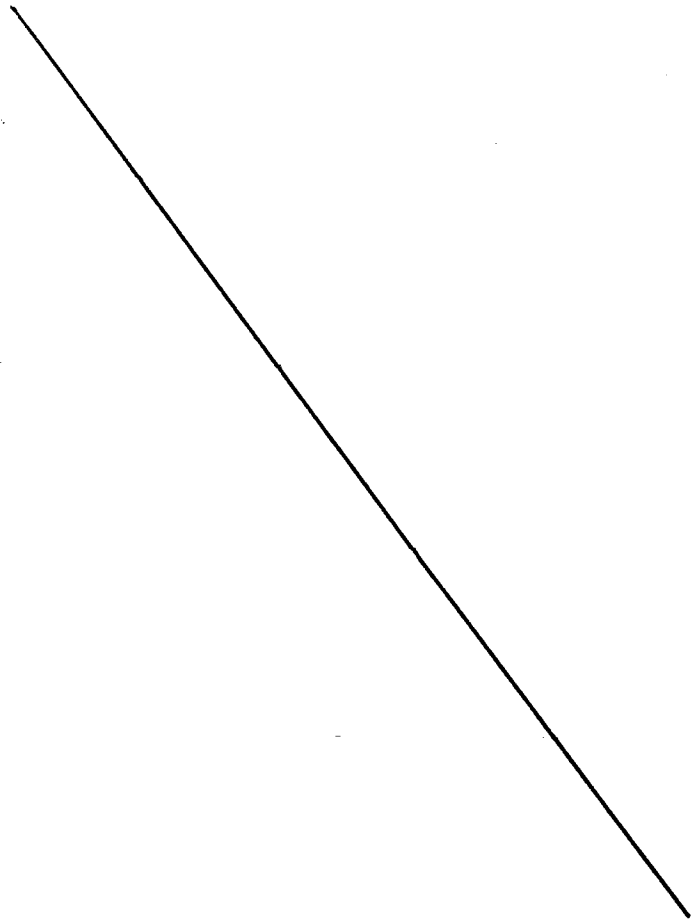
Clinical formulation: 5 mg tablets.

Daily Oral Dose: Children, 6-11 years old: 2.5-- mg; Adults, ≥ 12 years old: 5 mg.

Consult request by A. Shaw, Ph.D. on the safety of the proposed acceptance criterion of impurities/degradants in the levocetirizine drug product.

Evaluation

In the table below are - compounds that are impurities/degradants in the levocetirizine drug product. ——— The remaining - compounds are impurities/degradants resulting ——— of the drug product. The ICH Guidance Qualification Threshold for daily oral doses of impurities/degradants in a drug product which have a daily oral dose ≤ 10 mg is 1% or 50 ug whichever is lower. For a ——— the Threshold of Toxicologic Concern (TTC) is ——— The following table lists the daily doses of - compounds based on the proposed acceptance criteria. —— of them are below the ICH Qualification Guidance Threshold. The ——— is well below the TTC of ——. The ——— is acceptable since it is present ———



Recommendation

The proposed acceptance criterion for each of the / impurities/degradants in the 5 mg daily dose levocetirizine tablet from a PharmTox standpoint is acceptable.

Reviewer's signature: _____

Supervisor's signature:

Concurrence - _____

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/s/

Arthur B. Shaw
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Tox consult

Chemistry Review Cover Sheet

NDA 22-064
Xyzal™ (levocetirizine hydrochloride) Tablets
Arthur B. Shaw, Ph.D.
ONDQA/DPA1

Xyzal™
(levocetirizine dihydrochloride)
Tablets

NDA 22-064

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: UCB, Inc.
1950 Lake Park Drive
Smyrna GA 30080

Indication: symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 6 years of age and older.

Presentation: Xyzal is supplied as immediate release tablets that are white, film-coated, oval-shaped, scored, imprinted (with the letter Y in red color on both halves of the scored tablet). Each tablet contains 5 mg levocetirizine dihydrochloride; the scored tablet allows for the administration of a dose of 2.5 mg. Tablets are packaged in HDPE bottles (30 and 180 count) and in blisters (10 tablets per blister card, 3 cards per box).

EER Status: Acceptable 29-JAN-2007

Consults: Pharmacology/Toxicology - Acceptable 12-JAN-2007
Clinical Pharmacology - Acceptable 13-JUN-2006
EA – Categorical exclusion granted under 21 CFR §25.31(b).
Methods Validation – Revalidation by Agency not requested.

Original Submission: 24-JUL-2006

Post-Approval Agreements:
The applicant has agreed to submit the following additional information:
1. Complete polymorph screening. (CBE-30)
2. Updated methods validation reports. (CBE-30)
3. Updated test procedures to clarify when levocetirizine and when levocetirizine dihydrochloride are to be used. (Annual Report)

Drug Substance:

The drug substance, levocetirizine dihydrochloride, is the R-enantiomer of cetirizine hydrochloride and is known chemically as (R)–[2-[4-[(4-chlorophenyl) phenylmethyl- 1-piperazinyl]- ethoxy] acetic acid dihydrochloride. It has a molecular formula of $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$ and a molecular weight of 461.8 grams/mole. It is a white to off-

white powder that is freely soluble in water and slightly soluble in [redacted] It has three dissociation constants at pH 2.10, pH 3.05, and pH 8.35. It is not hygroscopic and does not exist as a polymorph.

[redacted] The [redacted] is a potential impurity in the drug and is controlled at NMT [redacted] by chiral HPLC.

The structure of levocetirizine dihydrochloride was elucidated using several analytical and spectrophotometric techniques, including [redacted] The absolute configuration is based on the absolute configuration of [redacted]

The proposed release specifications include appearance, identification by infrared (IR) and ultraviolet (UV) spectroscopy, enantiomeric purity by chiral HPLC, water content, residue on ignition, heavy metals, assay by HPLC and titration, achiral related substances by HPLC, chiral related substances by chiral HPLC, and residual solvents by gas chromatography. A reference standard for levocetirizine dihydrochloride has been developed and characterized.

[redacted] an impurity with [redacted] results from the use of [redacted] The proposed acceptance criterion of [redacted] will result in a level of [redacted] in the finished drug product. The pharmacology-toxicology consult review concluded this impurity content was acceptable.

Bulk drug substance, packed in sealed, [redacted] was shown to be stable for [redacted] years when stored at room temperature [redacted]

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is an immediate release tablet of 5 mg strength; each tablet contains 5 mg levocetirizine dihydrochloride. The tablets are white, film-coated, oval-shaped, and scored. Both halves of the scored tablet are imprinted with the letter Y in red. The scored tablet allows for the administration of a dose of 2.5 mg in pediatric populations.

The drug product is prepared by [redacted] The scored and unscored tablets have the same dissolution profiles and the half tablets meet Content Uniformity requirements.

The composition of the 5 mg strength tablet is levocetirizine dihydrochloride (5.00 mg), microcrystalline cellulose ——— colloidal anhydrous silica ———
lactose monohydrate ——— magnesium stearate ——— and ———
film coat ——— for total tablet weight of ———

Specifications for the drug product include: appearance; residual water content; identification by chiral and achiral HPLC; assay by achiral HPLC; content uniformity; dissolution of Q— at 30 minutes; and impurities by chiral and achiral HPLC. All test methods have been appropriately validated for their intended purpose.

Stability data support the requested 36 month expiration date for the drug product packaged in HDPE bottles (30 and 180 count) and in blisters (10 tablets per blister card, 3 cards per box) and stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Conclusion: Drug product is satisfactory.

Additional Items:

Two post-approval changes are proposed under a Comparability Protocol.

- The sponsor has proposed a number of changes in the manufacturing procedure.
- The sponsor has proposed a change in the manufacturing site, including the MMC chromatographic separation of the enantiomers, that will not be implemented until the first change is submitted and implemented.

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
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Withheld Track Number: Chemistry- 1

Chemistry Review Data Sheet

1. NDA 22064
2. REVIEW #2
3. REVIEW DATE: May 21, 2007
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

Document	Document Date	Comment
Original	24-Jul-2006	
Amendment	31-Aug-2006	Add drug product stability testing site
Amendment	20-Dec-2006	Add polymorph for intermediate
IR Fax	05-Jan-2007	Request Methods TDAAM0231 and TDAAM0176 Request info on compendial methods for excipients
Amendment	15-Jan-2007	Response to 05-Jan-2007 Request
Amendment	22-Jan-2007	Labeling
Discipline review Letter	24-Jan-2007	No approvability issues
IR Fax	26-Jan-2007	Request info on additional blister MBR for drug substance Updated stability data Shipping info for bulk drug product
Chem Review #1	06-Feb-2007	No approvability issues
IR E-mail	20-Mar-2007	Request info about imprinting ink
IR E-mail	20-Apr-2007	Info on reprocessing, DS batch record and MV for drug product
IR E-mail	03-May-2007	Request filing dates and process for commitments

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date	Comment
Amendment	22-Jan-2007	Labeling
Amendment	09-Feb-2007	Response to 26-Jan-2007 Request
Amendment	21-Mar-2007	Response to 20-Mar-2007 Request
Amendment	02-Apr-2007	Response to DR Letter
Amendment	23-Apr-2007	Drug substance batch record
Amendment	26-Apr-2007	Response to 20-Apr-2007 e-mail
Revised Label	02-May-2007	Revision in structure
Amendment	15-May-2007	Update post-approval agreements

7. NAME & ADDRESS OF APPLICANT:

Name: UCB, Inc.
Address: 1950 Lake Park Drive
Smyrna GA 30080

Representative: Susan Tegtmeyer
Telephone: 770-970-8654

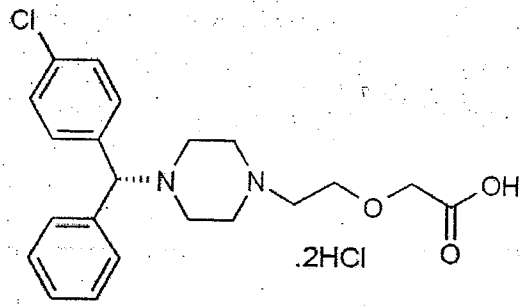
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Xyzal
   b) Non-Proprietary Name (USAN): levocetirizine
   c) Chem. Type/Submission Priority
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505(b)2

Reference Drug: Zyrtec (cetirizine hydrochloride) tablets NDA 19835.

10. PHARMACOL. CATEGORY: antihistamine
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 5 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Levocetirizine dihydrochloride

(R)–[2-[4-[(4-chlorophenyl) phenylmethyl- 1-piperazinyl]- ethoxy] acetic acid dihydrochloride



Code= ucb 28556
CAS = 130018-87-0
Molecular Formula: $C_{21}H_{25}N_2O_3Cl\,2HCl$
Molecular weight = 461.8

This structure is now included in the label (02-May-2007). **ACCEPTABLE**

17. RELATED/SUPPORTING DOCUMENTS:

PreIND 72233

NDAs 19835 (5 mg and 10 mg tablets)

—— (oral syrup 5 mg/mL)

21621 (chewable tablets, 5 and 10 mg)

A. DMFs:

Reviewed Type III, Adequate

DMF #	HOLDER	ITEM REFERENCED	DATE REVIEW COMPLETED
			30-Jan-2007
			30-Jan-2007
			01-Feb-2007
			01-Feb-2007

No other DMFs needed to be reviewed since adequate information about the materials is provided in the NDA.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Toxicology	Impurities **ACCEPTABLE**	12-Jan-2007	Lawrence Sancilio
DMETS	Proprietary name **ACCEPTABLE**	06-Apr-2007	Loretta Holmes
EA	Categorical exclusion granted	N/A	N/A
EES	Adequate for all sites	29-Jan-2007	

The Chemistry Review for NDA 22064

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved in terms of Chemistry, Manufacturing, and Controls. All manufacturing sites were found acceptable by the Office of Compliance (January 29, 2007)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance:

Levocetirizine dihydrochloride is the R-enantiomer of cetirizine hydrochloride, which is the active ingredient in the approved product, Zyrtec. The R enantiomer is reported to be responsible for the activity of cetirizine as an H_1-histamine receptor antagonist The S-enantiomer is reported to have a 30-fold lower affinity for the human H_1-histamine receptor. Batches of drug substance prepared using this method were used for the initial studies.

Preparation of the drug substance for commercial use will be by the same but the R-enantiomer will be There are no polymorphs reported for the levocetirizine dihydrochloride, but a complete polymorph screen was not performed. The applicant has committed to providing .

this information in a CBE-30 supplement. It is freely soluble in water. The S-isomer is controlled at the level of —— Individual identified impurities are controlled at NMT —— Individual unidentified impurities are controlled at NMT —— Total impurities are controlled at NMT —— An impurity ——— ——— ———

——— This was consulted to pharm/tox and found acceptable. The proposed acceptance criterion of ——— will result in a level of —— in the finished drug ———The specifications are supported by batch analysis. The test methods have been validated. The drug substance is stable at—— and will be stored at ——— with a retest period of — years

2. Drug Product

The drug product is a scored, film-coated 5 mg tablet with a red imprint "Y" on either side of the score. The core table is prepared ——————— ———————. There is no significant pharmaceutical development report, except to show that the scored and unscored tablets have the same dissolution profiles and that the half tablets meet Content Uniformity requirements.\ The specifications, including a dissolution specification of Q= — at 30 minutes, are supported by batch analysis. The test methods have been validated. The impurities are adequately controlled and qualified. The stability data was collected using the tablets without imprinting and supports a 36 month expiration date for drug product packaged in 15 mL and 50 mL bottles, ——— blisters, and ——————— blisters.

There is no stability data for the imprinted formulation but this is will be provided in the Annual Reports.

B. Description of How the Drug Product is Intended to be Used

The drug is intended to be dosed orally once a day for treatment of symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 6 years of age and older.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is manufactured and controlled adequately.

III. **Administrative** Signed off in DFS

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Arthur B. Shaw
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CMC Review

Blair Fraser
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Chemistry Review Cover Sheet

NDA 22-064
Xyzal™ (levocetirizine hydrochloride) Tablets
Arthur B. Shaw, Ph.D.
ONDQA/DPA1

Chemistry Review Data Sheet

1. NDA 22064
2. REVIEW #1
3. REVIEW DATE: February 1, 2007
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date	Comment
Original	24-Jul-2006	
Amendment	31-Aug-2006	Add drug product stability testing site
Amendment	20-Dec-2006	Add polymorph for intermediate
Amendment	22-Jan-2007	Labeling
Amendment	24-Jan-2007	Response to IR

7. NAME & ADDRESS OF APPLICANT:

Name: UCB, Inc.
Address: 1950 Lake Park Drive
Smyrna GA 30080
Representative: Susan Tegtmeyer
Telephone: 770-970-8654

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Xyzal
   b) Non-Proprietary Name (USAN): levocetirizine
   c) Chem. Type/Submission Priority
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505(b)2

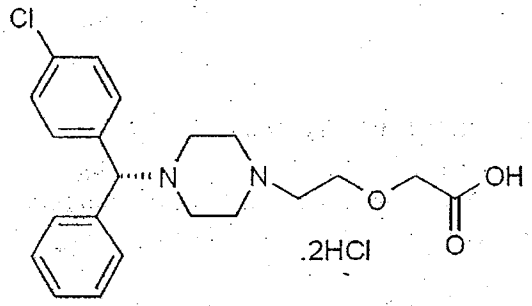
Reference Drug: Zyrtec (cetirizine hydrochloride) tablets NDA 19835.

10. PHARMACOL. CATEGORY: antihistamine
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 5 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Levocetirizine dihydrochloride

(R)–[2-[4-[(4-chlorophenyl) phenylmethyl- 1-piperazinyl]- ethoxy] acetic acid dihydrochloride



Code= ucb 28556
CAS = 130018-87-0
Molecular Formula: $C_{21}H_{25}N_2O_3Cl{\cdot}2HCl$
Molecular weight = 461.8

17. RELATED/SUPPORTING DOCUMENTS:

PreIND 72233
NDAs 19835 (5 mg and 10 mg tablets)
[redacted] (oral syrup 5 mg/mL)
21621 (chewable tablets, 5 and 10 mg)

A. DMFs:

Reviewed Type III, Adequate

DMF #	HOLDER	ITEM REFERENCED	DATE REVIEW COMPLETED
[redacted]			30-Jan-2007
			30-Jan-2007
			01-Feb-2007
			01-Feb-2007

No other DMFs needed to be reviewed since adequate information about the materials is provided in the NDA.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Toxicology	Request sent for impurities	12-Jan-2007	Lawrence Sancilio
DMETS	Proprietary name under review	29-Nov-2006	Pending
EA	Categorical exclusion granted	N/A	N/A
EES	Adequate for all sites	01-Dec-2006	

The Chemistry Review for NDA 22064

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable in terms of Chemistry, Manufacturing, and Controls pending responses to the questions in the draft information request letter. All manufacturing sites were found acceptable by the Office of Compliance (December 1, 2006)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance:

Levocetirizine dihydrochloride is the R-enantiomer of cetirizine hydrochloride, which is the active ingredient in the approved product, Zyrtec. The R enantiomer is reported to be responsible for the activity of cetirizine as a H_1-histamine receptor antagonist The S-enantiomer is reported to have a 30-fold lower affinity for the human H_1-histamine receptor. ——— Batches of drug substance prepared using this method were used for the initial studies.

Preparation of the drug substance for commercial use will be by the same ——— but the R-enantiomer will be ——— There are no polymorphs for the levocetirizine dihydrochloride. It is freely soluble in water. . The S-isomer is controlled at the level of ——— Individual identified impurities are controlled at NMT——— Individual unidentified impurities are controlled at NMT ——— Total impurities are controlled at NMT ——— An impurity , ——— This has been consulted to pharm/tox. The proposed acceptance criterion of ——— will result in a level of ——— in the finished drug product. The specifications are supported by batch analysis. The test methods have been validated. The drug substance is stable at ——— and will be stored at ——— with a retest period of ——— years

2. Drug Product

The drug product is a scored, film-coated 5 mg tablet. It is prepared by ——— There is no significant pharmaceutical development report, except to show that the scored and unscored tablets have the same dissolution profiles and that the half tablets meet Content Uniformity requirements.\ The specifications, including a dissolution specification of Q= — at 30 minutes, are supported by batch analysis. The test methods have been validated. The impurities are adequately controlled. The stability data support a 36 month expiration date for drug product packaged in 15 mL bottles, one type of ——— blisters, and ——— blisters. Data to support expiration dating in 50 mL bottles and another type of ——— blisters.

B. Description of How the Drug Product is Intended to be Used

The drug is intended to be dosed orally once a day for treatment of symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 6 years of age and older.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is manufactured and controlled adequately. Clarification of some controls is being requested.

III. **Administrative** Signed off in DFS

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