CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-157

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 22-157

XYZAL® (levocetirizine dihydrochloride) Oral Solution

UCB, Inc.

Craig M. Bertha, Ph.D.
ONDQA for DPAP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-157

2. REVIEW #:3

3. REVIEW DATE: 03-DEC-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	27-MAR-2007
Amendment	18-JUL-2007 (assigned 25-JUL-2007)
Amendment	27-JUN-2007 (assigned 05-JUL-2007)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	26-SEP-2007 (consult to pharm./tox.)
Amendment	06-NOV-2007 (assigned 14-NOV-2007)
Amendment (labeling)	13-NOV-2007 (assigned 23-NOV-2007)

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: XYZAL®
b) Non-Proprietary Name (USAN): levocetirizine dihydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: antihistamine

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 0.5 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

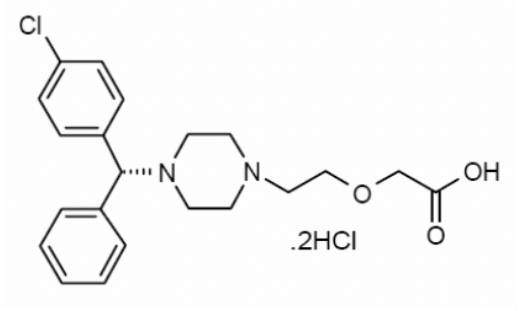
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

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

Chemistry Review Data Sheet



Code= ucb 28556
CAS = 130018-87-0
Molecular Formula: $C_{21}H_{25}N_2O_3Cl2HCl$
Molecular weight = 461.8

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	Adequate	10-APR-2007	
	3			3	Adequate	12-APR-2007	
	3			3	Adequate	23-AUG-2007 111-OCT-2007	
	3			3	Adequate	07-JAN-2004	No product contact
	3			4	N/A		No product contact
	3			3	Adequate	08-NOV-2006	
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3				Adequate	06-JUN-2007	
	3			1	Adequate	10-APR-2007	
	3			3	Adequate	23-JUN-2006	Reviewed for solid oral; no product contact
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3			3	Adequate	29-JAN-2003	Reviewed for (b) (4) for oral administration

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	72,233	UCB	IND for both tablet and oral solution dosage forms of levocetirizine dihydrochloride
NDA	22-064	UCB	Referenced for all information/data supporting the drug substance levocetirizine dihydrochloride

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A see P.8.3 evaluation
EES	cGMP compliance/PAI	05-APR-2007	Acceptable	OC decision dated 09-APR-2007
Pharm/Tox	Leachables/extractables consults	09-JUL-2007 26-SEP-2007	Final Pending	(b) (4) [redacted]
Biopharm				N/A
LNC				N/A
Methods Validation				Not needed.
DMETS				DPAP will forward consult.
EA				N/A see p. 53 of CR#1.
Microbiology	Microbial limits, preservative effectiveness testing, and preservative assay acceptance criteria	06-APR-2007	Pending	Microbial limits acceptance criteria appear to be inconsistent relative to the recommendations of USP <1111>

The Chemistry Review for NDA 22-157

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval**.

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]

The drug substance is levocetirizine dihydrochloride which is the R-enantiomer of cetirizine hydrochloride (actually a dihydrochloride as well, but not reflected in USAN name), the active ingredient in the approved Zyrtec® antihistamine products (Pfizer). The R-enantiomer is purported to be responsible for the activity of cetirizine as a H1-histamine receptor antagonist. The applicant states that the S-enantiomer has a 30-fold lower affinity for the human H1-histamine receptor. The R-enantiomer was originally isolated by a (b) (4) but later the applicant used (b) (4) system by the applicant] for the (b) (4) of the racemate.

There are no polymorphs for the levocetirizine dihydrochloride and it is freely soluble in water. The (b) (4) is controlled to a level of (b) (4)% or less. Individual identified impurities are controlled to NMT (b) (4)% and individual unidentified impurities are controlled to NMT (b) (4)%. There is a limit for the total impurities of NMT (b) (4)%. The drug substance specifications are said to be supported by batch analysis (review of N22-064) and the test methods have been validated by the applicant. The drug substance is stable at 40°C and will be stored at 15-30°C with a retest period of (b) (4)

The drug product is an oral solution formulated at a target pH of 5.0. The formulation contains 0.5 mg levocetirizine dihydrochloride/mL and the maximum daily dosage proposed is 5.0 mg. The aqueous-based drug product formulation is (b) (4) by (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

[1] The summary drug substance information was abstracted from the chemistry review #1 from Dr. Art Shaw for NDA 22-064. All drug substance information in NDA 22-157 is referenced to NDA 22-064.

samples. The drug product formulation as packaged is demonstrated to have adequate stability to support a 24 month expiration dating period.

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

The drug product is intended to be dosed orally once a day at either a 2.5 mg or 5.0 mg dose for adults and children 6 years and older.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/12/03/07
AAl-Hakim/ONDQA/DIV I/Branch Chief_____

C. CC Block

LGarcia/DPAP/Regulatory PM
PPeri/ONDQA/DIV I/Branch II/PAL
SGoldie/ONDQA/DIV I

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

/s/

Craig Bertha
12/3/2007 07:57:38 AM
CHEMIST

Blair Fraser
12/3/2007 08:01:27 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-157

XYZAL® (levocetirizine dihydrochloride) Oral Solution

UCB, Inc.

Craig M. Bertha, Ph.D.
ONDQA for DPAP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-157

2. REVIEW #:2

3. REVIEW DATE: 31-JUL-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	27-MAR-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	18-JUL-2007 (assigned 25-JUL-2007)
Amendment	27-JUN-2007 (assigned 05-JUL-2007)

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: XYZAL®
b) Non-Proprietary Name (USAN): levocetirizine dihydrochloride
c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: antihistamine

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 0.5 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

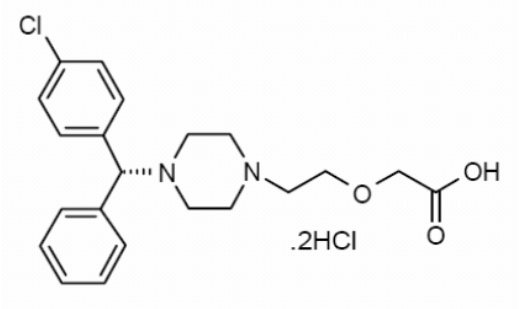
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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: $C_{21}H_{25}N_2O_3Cl2HCl$
Molecular weight = 461.8

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	4		(b) (4)	1	Adequate	10-APR-2007	
	3			3	Adequate	12-APR-2007	
	3			3	Adequate	07-JAN-2004	
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3			3	Adequate	08-NOV-2006	
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3				Adequate	06-JUN-2007	
	3			1	Adequate	10-APR-2007	
	3			3	Adequate	23-JUN-2006	Reviewed for solid oral; no product contact
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3			3	Adequate	29-JAN-2003	Reviewed for (b) (4) for oral administration

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	72,233	UCB	IND for both tablet and oral solution dosage forms of levocetirizine dihydrochloride
NDA	22-064	UCB	Referenced for all information/data supporting the drug substance levocetirizine dihydrochloride

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A see P.8.3 evaluation
EES	cGMP compliance/PAI	05-APR-2007	Acceptable	OC decision dated 09-APR-2007
Pharm/Tox	Leachables/extractables consult	09-JUL-2007	Pending	
Biopharm				N/A
LNC				N/A
Methods Validation				Not needed.
DMETS				DPAP will forward consult.
EA				N/A see p. 53 of CR#1.
Microbiology	Microbial limits, preservative effectiveness testing, and preservative assay acceptance criteria	06-APR-2007	Pending	Microbial limits acceptance criteria appear to be inconsistent relative to the recommendations of USP <1111>

The Chemistry Review for NDA 22-157

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval**. However, the consult to the pharmacology/toxicology team regarding the leachables/extractables is pending and depending on their conclusions of safety, there may need to be additional controls put in place. Also, the consult to the microbiological team is also pending. The outcome of this review may also impact on the CMC requirements for the application.

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

None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)[1]

The drug substance is levocetirizine dihydrochloride which is the R-enantiomer of cetirizine hydrochloride (actually a dihydrochloride as well, but not reflected in USAN name), the active ingredient in the approved Zyrtec® antihistamine products (Pfizer). The R-enantiomer is purported to be responsible for the activity of cetirizine as a H1-histamine receptor antagonist. The applicant states that the S-enantiomer has a 30-fold lower affinity for the human H1-histamine receptor. The R-enantiomer was originally (b) (4) but later the applicant used (b) (4) system by the applicant] for the (b) (4) of the racemate.

There are no polymorphs for the levocetirizine dihydrochloride and it is freely soluble in water. The (b) (4) is controlled to a level of (b) (4)% or less. Individual identified impurities are controlled to NMT (b) (4)% and individual unidentified impurities are controlled to NMT (b) (4)%. There is a limit for the total impurities of NMT (b) (4)%. The drug substance specifications are said to be supported by batch analysis (review of N22-064) and the test methods have been validated by the applicant. The drug substance is stable at 40°C and will be stored at 15-30°C with a retest period of (b) (4)

[1] The summary drug substance information was abstracted from the chemistry review #1 from Dr. Art Shaw for NDA 22-064. All drug substance information in NDA 22-157 is referenced to NDA 22-064.

The drug product is an oral solution formulated at a target pH of 5.0. The formulation contains 0.5 mg levocetirizine dihydrochloride/mL and the maximum daily dosage proposed is 5.0 mg. The aqueous-based drug product formulation is (b) (4) by (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 (b) (4) bottles for marketing and there will also be 15 mL amber glass (b) (4) bottles for physician samples. The drug product formulation as packaged is demonstrated to have adequate stability to support a 24 month expiration dating period.

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

The drug product is intended to be dosed orally once a day at either a 2.5 mg or 5.0 mg dose for adults and children 6 years and older.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/7/31/07
AAl-Hakim/ONDQA/DIV I/Branch Chief_____

C. CC Block

LGarcia/DPAP/Regulatory PM
PPeri/ONDQA/DIV I/Branch II/PAL
SGoldie/ONDQA/DIV I

12 Pages Withheld in Full Immediately After This Page as (b)(4) CCI/TS.

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

/s/

Craig Bertha
8/7/2007 05:19:14 AM
CHEMIST

Ali Al-Hakim
8/7/2007 11:04:59 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-157

XYZAL® (levocetirizine dihydrochloride) Oral Solution

UCB, Inc.

Craig M. Bertha, Ph.D.
ONDQA for DPAP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-157

2. REVIEW #:1

3. REVIEW DATE: 19-APR-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-MAR-2007 (assigned 03-APR-2007)

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: XYZAL®
b) Non-Proprietary Name (USAN): levocetirizine dihydrochloride
c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: antihistamine

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 0.5 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

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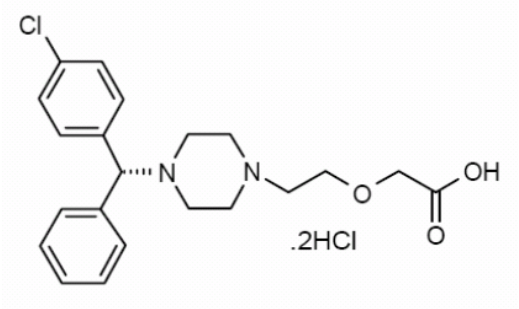
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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



Code= ucb 28556

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Molecular Formula: $C_{21}H_{25}N_2O_3Cl2HCl$
Molecular weight = 461.8

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	3			3	Adequate	12-APR-2007	
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3				3	08-NOV-2006	
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3				**Inadequate**	12-APR-2007	Deficiency letter sent
	3			1	Adequate	10-APR-2007	
	3			3	Adequate	23-JUN-2006	Reviewed for solid oral; no product contact
	3			4	N/A		No product contact
	3			4	N/A		No product contact
	3			3	Adequate	29-JAN-2003	Reviewed for (b) (4) for oral administration

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[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

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NDA	22-064	UCB	Referenced for all information/data supporting the drug substance levocetirizine dihydrochloride

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A see P.8.3 evaluation
EES	cGMP compliance/PAI	05-APR-2007	Acceptable	OC decision dated 09-APR-2007
Pharm/Tox				A consult on extractables/leachables may be needed depending on applicant responses.
Biopharm				N/A
LNC				N/A
Methods Validation				Will be submitted once the appropriate revisions are made to the application.
DMETS				DPAP will forward consult.
EA				N/A see p. 53.
Microbiology	Microbial limits, preservative effectiveness testing, and preservative assay acceptance criteria	06-APR-2007	Pending	Microbial limits acceptance criteria appear to be inconsistent relative to the recommendations of USP <1111>

The Chemistry Review for NDA 22-157

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is currently considered to be **approvable**, pending the resolution of the CMC issues outlined in the attached deficiency letter.

The PM is requested to forward the comments in the attached draft letter to the applicant once the Agency files the application.

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

No recommendation at this time pending applicant's response to deficiency letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)[1]

The drug substance is levocetirizine dihydrochloride which is the R-enantiomer of cetirizine hydrochloride (actually a dihydrochloride as well, but not reflected in USAN name), the active ingredient in the approved Zyrtec® antihistamine products (Pfizer). The R-enantiomer is purported to be responsible for the activity of cetirizine as a H1-histamine receptor antagonist. The applicant states that the S-enantiomer has a 30-fold lower affinity for the human H1-histamine receptor. The R-enantiomer was originally (b) (4) but later the applicant used (b) (4) system by the applicant] for the (b) (4) of the racemate.

There are no polymorphs for the levocetirizine dihydrochloride and it is freely soluble in water. The (b) (4) is controlled to a level of (b) (4)% or less. Individual identified impurities are controlled to NMT (b) (4)% and individual unidentified impurities are controlled to NMT (b) (4)%. There is a limit for the total impurities of NMT (b) (4)%. The drug substance specifications are said to be supported by batch analysis (review of N22-064) and the test methods have been validated by the applicant. The drug substance is stable at 40°C and will be stored at 15-30°C with a retest period of (b) (4)

The drug product is an oral solution formulated at a target pH of 5.0. The formulation contains 0.5 mg levocetirizine dihydrochloride/mL and the maximum daily dosage proposed is 5.0 mg.

[1] The summary drug substance information was abstracted from the chemistry review #1 from Dr. Art Shaw for NDA 22-064. All drug substance information in NDA 22-157 is referenced to NDA 22-064.

The aqueous-based drug product formulation is [redacted] (b) (4) and also includes maltitol solution, glycerin, saccharin [redacted] (b) (4) methylparaben and propylparaben, and [redacted] (b) (4) flavoring. The product will be packaged in 5 oz. (148 mL) amber glass [redacted] (b) (4) bottles for marketing and there will also be 15 mL amber glass [redacted] (b) (4) bottles for physician samples. The drug product formulation as packaged is demonstrated to have adequate stability to support a 24 month expiration dating period.

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

The drug product is intended to be dosed orally once a day at either a 2.5 mg or 5.0 mg dose for adults and children 6 years and older.

C. Basis for Approvability or Not-Approval Recommendation

In addition to the resolution of the issues outlined in the attached deficiency letter, the approvability of the application is dependent on the approvability of the related NDA 22064, which is referenced for all drug substance information and data.

With regard to the CMC information provided in support of the drug product, there are deficiencies involving the studies characterizing the extractables/leachables from the [redacted] (b) (4) containers. In addition, there are questions regarding the suitability of the proposed method for the determination of the degradants in the drug product. Other issues are captured in the attached deficiency letter (see p. 54) that will be forwarded to the applicant.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/4/19/07
BFraser/ONDQA/DIV I/Division Director_____

C. CC Block

LGarcia/DPAP/Regulatory PM
PPeri/ONDQA/DIV I/Branch II/PAL
SGoldie/ONDQA/DIV I

46 Pages Withheld In Full Immediately After this Page as (b)(4) CCI/TS.

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

/s/

Craig Bertha
4/19/2007 11:04:14 AM
CHEMIST

See hardcopy in your inbox

Blair Fraser
4/20/2007 05:30:41 PM
CHEMIST