15. Regarding the Environmental Assessment:

    a. Please check the calculation of the Expected Introduction Concentration (EIC).

16. Contact the DMF holders for DMFs [redacted] and request that they submit new LOAs to the DMFs. We will accept faxed copies or e-mail attachments from the holders in addition to the official paper copy of the submission. The LOA for DMF [redacted] must specify the item to be reviewed and the date and page where the information can be found. Alternatively, provide a statement that the materials from these suppliers meet appropriate food contact regulations, specifying the name of the referenced material and the specific CFR section.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Blair A. Fraser, Ph.D.
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
2/27/2007 06:54:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

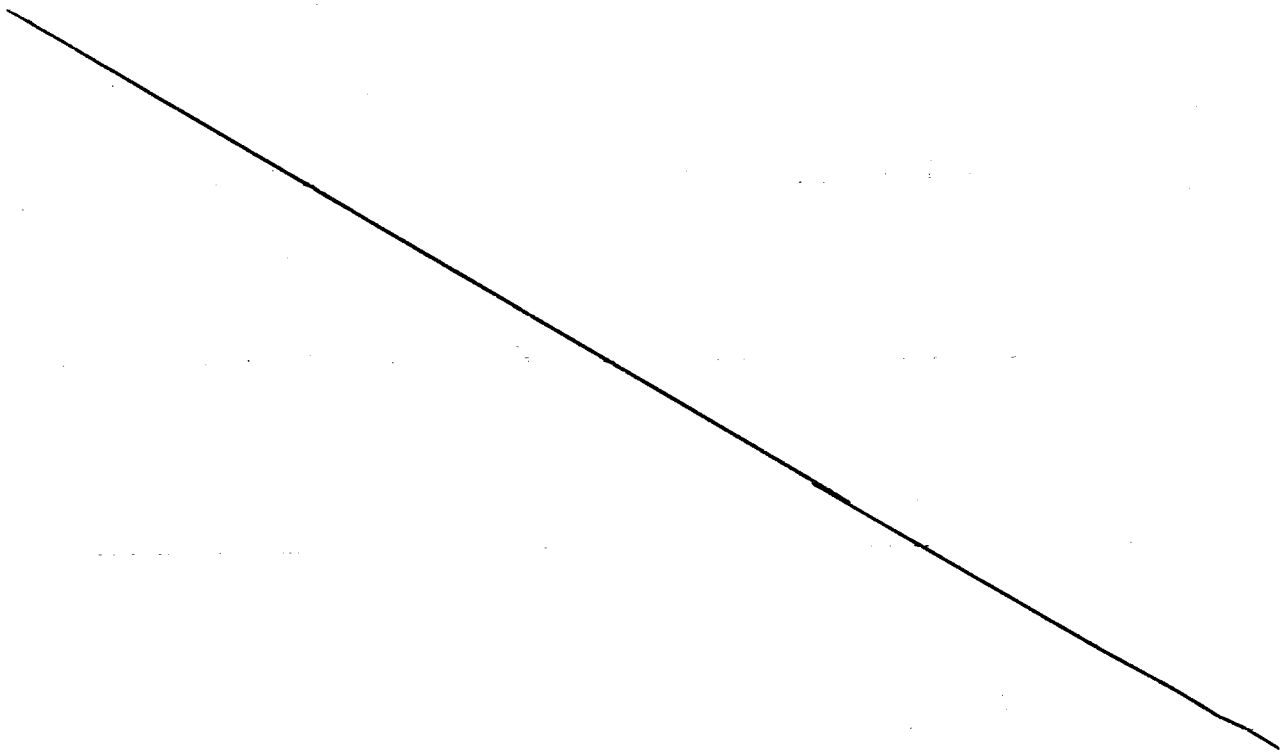
Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5mg Tablets.

We also refer to your submissions dated August 31 and December 20, 2006, and January 15 and 22, 2007.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:



7 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3

15. Regarding the Environmental Assessment:

    a. Please check the calculation of the Expected Introduction Concentration (EIC).

16. Contact the DMF holders for DMFs [redacted] and request that they submit new LOAs to the DMFs. We will accept faxed copies or e-mail attachments from the holders in addition to the official paper copy of the submission. The LOA for DMF[redacted] must specify the item to be reviewed and the date and page where the information can be found. Alternatively, provide a statement that the materials from these suppliers meet appropriate food contact regulations, specifying the name of the referenced material and the specific CFR section.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Blair A. Fraser, Ph.D.
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
2/27/2007 06:54:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

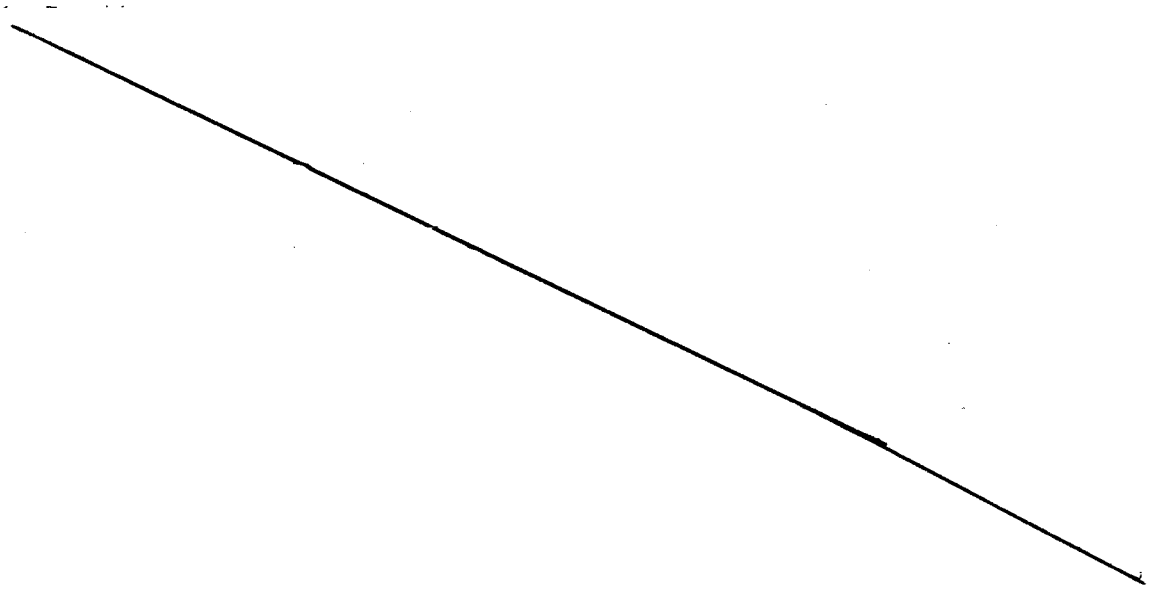
UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5mg Tablet.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.



If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
1/24/2007 05:33:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5mg Tablet.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

Drug Product

2. Regarding the excipients: Citation of the Ph. Eur. monographs is not sufficient to ensure the quality of the excipients for the purposes of an NDA in the United States. If you do not provide information in the NDA demonstrating that the excipients meet the specifications in their respective NF monographs, and that they will be tested against those monographs for each incoming batch, the Ph. Eur. monographs will be considered for acceptability if you provide the following information:

    a. A side-by-side comparison of the Ph. Eur. monographs with the NF monographs.

    b. A scientific rationale for accepting the excipient based on the Ph. Eur. Monograph if there are tests and acceptance criteria in a Ph. Eur. monograph that are not the same as those in the NF monograph.

    c. The full text and validation information for the test procedures in the Ph. Eur.

monograph if there are test procedures in the Ph. Eur. monograph that differ from the corresponding test in the NF monograph,

d. A commitment to report any changes in the monographs or test procedures to the NDA, both pre-and post-approval, including adequate supporting data to qualify the change.

Impurities

[redacted]

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
1/5/2007 05:25:25 PM

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

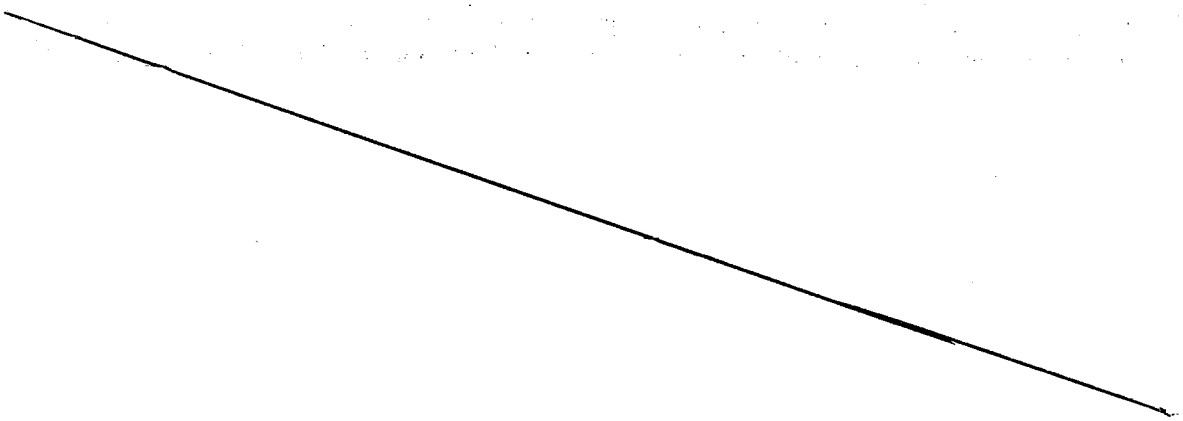
Date: December 22, 2006

From: Arthur B. Shaw, Ph.D., Chemist, Division of Pulmonary and Allergy Drug Products, HFD-570

To: NDA 22064

Subject: Information Requests

A number of issues have been identified in the review of this NDA that should be communicated to the applicant before the review is complete.



Drug Product

Excipients
The applicant accepts the excipients (except the coating) on the basis of a CoA and meeting Ph.Eur. specifications. They have provided COAs and copies of the Ph. Eur. monographs. However the applicant has not provided a comparison between the Ph.Eur. and USP/NF specifications.
COMMENT: Citation of the Ph. Eur. monographs is not sufficient to ensure the quality of the excipients for the purposes of an NDA in the US. If you do not provide information in the NDA that the excipients meet the specifications in their respective NF monographs and that they will be tested against those monographs for each incoming batch, the Ph. Eur. monographs will be considered for acceptability if you provide the following information:

Impurities

Draft Letter to the Applicant:

Regarding the drug product

Regarding the excipients: Citation of the Ph. Eur. monographs is not sufficient to ensure the quality of the excipients for the purposes of an NDA in the US. If you do not provide information in the NDA that the excipients meet the specifications in their respective NF monographs and that they will be tested against those monographs for each incoming batch, the Ph. Eur. monographs will be considered for acceptability if you provide the following information:

a. A side-by-side comparison of the Ph. Eur. monographs with the NF monographs.
b. A scientific rationale for accepting the excipient based on the Ph. Eur. Monograph if there are tests and acceptance criteria in a Ph. Eur. monograph that are not the same as those in the NF monograph,
c. The full text and validation information for the test procedures in the Ph. Eur. monograph if there are test procedures in the Ph. Eur. monograph that differ from the corresponding test in the NF monograph,
d. A commitment to report any changes in the monographs or test procedures to the NDA, both pre-and post-approval, including adequate supporting data to qualify the change.

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/s/

Arthur B. Shaw
12/22/2006 09:21:57 AM
CHEMIST
Memo for CMC IR Letter

MEMORANDUM OF EMAIL COMMUNICATION

DATE: December 19, 2006

APPLICATION NUMBER: NDA 22-064

BETWEEN:

Name: Susan Tegtmeyer
Phone: Susan.Tegtmeyer@ucb-group.com
Representing: UCB, Inc.

AND

Name: Lori Garcia, R.Ph.
Division of Pulmonary and Allergy Products

SUBJECT:

From: Garcia, Lori
Sent: Tuesday, December 19, 2006 4:41 PM
To: 'Tegtmeyer Susan'
Subject: N22-064

Hi Susan,

We are in the process of reviewing your November 20, 2006, submission and note that you have not submitted ECGs to the ECG warehouse. Can you please submit the related ECGs to www.ecgwarehouse.com ?

The FDA Review Team requests that Sponsors have the ECG source data uploaded into the ECG Warehouse as part of the review process. The evaluation of the ECG waveform data will aide in assessing specific drug-induced cardiac toxicity by evaluating the data with detailed, sponsor-generated annotations from the ECG devices such as 12-lead standard ECG, Holter monitors, and implanted devices.

If you have any questions, please let me know,

Thanks,

LCDR Lori Garcia, R.Ph.
Regulatory Project Manager
FDA/CDER/OND/DPAP
Bldg. 22, Rm. 3343
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
Phone: (301) 796-1212
lori.garcia@fda.hhs.gov

Lori Garcia, R.Ph.
Regulatory Project Manager

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/s/

Lori Garcia
12/19/2006 04:58:09 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Office/Division): Division of Drug Marketing, Advertising and Communications

FROM (Name, Office/Division, and Phone Number of Requestor):
Lori Garcia, R.Ph., Regulatory Project Manager
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 28, 2006		NDA 22-064	Original NDA	July 24, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xyzal	standard		March 23, 2007

NAME OF FIRM: UCB, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please perform DDMAC review of new NDA 22-064 for Xyzal (levocetirizine) 5mg Tablets. The entire NDA is available in the EDR.
If you have any questions, please contact me at 301-796-1212.
PDUFA goal: May 25, 2007

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Lori Garcia	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Lori Garcia
11/29/2006 03:23:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for levocetirizine dihydrochloride (Xyzal) 5mg Tablets.

We are reviewing the Statistical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In your October 31, 2006, submission, it appears that you have provided in the T3SSsummary.pdf file for Study A00268, the results of the analysis of T4SS assessed over the last 24 hours and T3SS assessed over the last hour. Is this assessment correct? If so, provide the results of the analysis of T3SS assessed over the last 24 hours averaged over Week 1, averaged over Week 2, and averaged over the Total Two Week Treatment Period. If our assessment is not correct, explain what is contained in your analysis variables T3SS and T3SS24 in your datafiles effeff.xpt and effmeff.xpt in folder A00268 of the October 31, 2006, submission.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

/See appended electronic signature page/

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
11/27/2006 04:35:38 PM
signed for Sandy Barnes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5 mg Tablets.

We are reviewing the Clinical and Statistical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

CLINICAL

Clarify the following issues regarding Study A00269 (levocetirizine 5 mg daily vs. placebo in patients with chronic idiopathic urticaria):

Intention-to-treat (ITT) population:

a. In section 11.1 "Data Sets Analyzed," (p 49), the ITT population in Figure 11.1 is N = 166. Below the study scheme the text reads: "Demographic, efficacy and safety analyses were carried out on the ITT population."

b. In section 9.7.1.4 "Evaluation of Efficacy," (p 42), "The primary analysis dataset consisted of those subjects included in the ITT population and having at least one measurement for the daily pruritus severity, 24-hour evaluation, in the daily record card, during the baseline period and one measurement during the treatment period."

c. In section 9.7.1.1 "Study populations," (p 41), the text reads: "The Intention-to-Treat population (ITT) consists of all randomized subjects who took at least one dose of study medication."

d. In section 9.4.2 "Handling of Dropouts or Missing Data," (p 551), the text reads: "Thus an efficacy assessment is available for every patient if the patient completed

the daily record card at least once regardless whether the patient completed the treatment period or not."

e. In section 11.4 "Efficacy Results and Tabulations of Individual Subject Data," (pp 57-60), three tables (11:6, 11:7, and 11:10) purport to be results of analyses of the ITT population, yet the total N for each table does not equal 166 (the ITT population N given in section 11.1), and the total N in each of the three efficacy tables cited are not equivalent.

1. Clarify your definition of the ITT population. If it is a different number than stated in the study (N = 166), explain the discrepancy.

2. Explain the discrepancy between the ITT population N = 166 (cited in section 11.1) and the ITT numbers given in Table 11:6 (161), Table 11:7 (162), and Table 11:10 (142, 130, and 125). In explaining these various ITT numbers, clarify how your explanation is consistent with the statements made in clauses b, c, and d, above.

STATISTICAL

3. In our letter dated September 22, 2006, the Division requested a reanalysis of studies A00266, A00268, A00303, A00304, and A00265 using total nasal symptom score (TNSS) which did not include "ocular pruritus". For these studies, provide analysis datasets similar to EFFEFF and EFFMEFF previously provided. These new datasets need only contain individual daily scores, Baseline and on-treatment averages for TNSS (baseline, week means, total period means, and other weekly summaries) for both the ITT and PP populations.

4. Provide similar analysis datasets for TNSS for Study A222.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
11/7/2006 03:39:28 PM
signed for Sandy Barnes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for levocetirizine dihydrochloride (Xyzal) 5mg Tablets.

We are reviewing the Clinical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding study A00412, we note that in the study results table 11.4 on page 67 of the study report, the mean Baseline (SD) for each treatment group ranges between 15.94 (5.76) and 16.36 (6.17). These values appear to be inconsistent with the baseline entry criteria described in the protocol (at least 18). Clarify this discrepancy, and/or re-do the efficacy analysis with the correct baseline.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
11/2/2006 11:05:18 AM
CSO
signed for Sandy Barnes

DSI CONSULT: Request for Clinical Inspections

Date: October 26, 2006

To: Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Gary Della'Zanna, Director, DSI, HFD-45
Badrul Chowdhury, M.D., Ph.D., Director, HFD-570 (for foreign inspection requests)

From: Lori Garcia, Regulatory Project Manager, HFD-570
Division of Pulmonary and Allergy Products

Subject: **Request for Clinical Site Inspections**
NDA 22-064
UCB Pharma, Inc.
Xyzal (levocetirizine dihydrochloride) 5 mg Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects**(see datafiles sent via email)	Indication
Paul Potter UCT Lung Institute Corner George & Falmouth Roads 7925 Observatory Western Cape South Africa	A00266		
Christiaan T. De Villiers 20 David Street Scottburgh South 4180 KwaZulu Natal South Africa	A00266		

Site # (Name and Address)	Protocol #	Number of Subjects**(see datafiles sent via email)	Indication
Adam Viljoen 1007 Louis Pasteur Building Schoeman Street Pretoria, 0002 Gauteng South Africa	A00268		

Domestic Inspections:

We have requested inspections because (please check all that apply):

____ Enrollment of large numbers of study subjects

____ High treatment responders (specify:)

____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

____ Other: SPECIFY

International Inspections:

We have requested inspections because (please check all that apply):

____ There are insufficient domestic data

__X__ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by March 23, 2007. We intend to issue an action letter on this application by May 25, 2007. The PDUFA due date for this application is May 25, 2007.

Should you require any additional information, please contact Lori Garcia.

Concurrence:

Lydia Gilbert-McClain, MD, Medical Team Leader
Robert Boucher, MD, MPH, Medical Reviewer
Badrul A. Chowdhury, MD, PhD, Division Director (for foreign inspection requests only)

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/s/

Lori Garcia
10/31/2006 03:10:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5mg Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide an established name for the compound recognized by the United States Adopted Name (USAN) Council.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Blair A. Fraser, Ph.D
Chief, Branch II
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
10/31/2006 03:25:51 PM

MEMORANDUM OF E-MAIL COMMUNICATION

DATE: October 23, 2006

APPLICATION NUMBER: NDA 22-064

BETWEEN:

Name:	Susan Tegtmeyer
e-mail address:	Susan.Tegtmeyer@ucb-group.com
Representing:	UCB, Inc.

AND

Name:	Lori Garcia, R.Ph., Regulatory Project Manager Division of Pulmonary and Allergy Products

SUBJECT: CMC question regarding location of data in NDA. See e-mail (attached).

Lori Garcia, R.Ph.
Regulatory Project Manager

E-MAIL ATTACHMENT

Lori,

The information requested is provided in Module 3 Section 3.2.P, Page 11 of 635 in Table 3:3: Levocetirizine 5mg Tablet Batch Disposition and Relationship to Drug Substance Batches and on Page 10 of 635 (same Module/section) in Table 3:2: Clinical Formulations.

Regards,
Susan

-----Original Message-----
From: Tegtmeyer Susan
Sent: Monday, October 23, 2006 8:25 AM
To: 'Garcia, Lori'
Subject: RE: N22-064

Hi Lori,
I have forwarded the request to our CMC group and will provide the information asap.

Also FYI, we are planning to submit the ISE and the efficacy datasets tomorrow. The reanalysis of the TNSS that was requested in the RTF letter is targeted for submission by the end of the month.
Regards,
Susan

-----Original Message-----
From: Garcia, Lori [mailto:lori.garcia@fda.hhs.gov]
Sent: Sunday, October 22, 2006 8:20 PM
To: Tegtmeyer Susan
Subject: N22-064

Hi Susan,

Our CMC reviewer is looking for the following information in the NDA:

* A listing of the batch numbers of drug product used in different clinical, pre-clinical, and stability studies, including the batch numbers of the drug substance used to manufacture those batches of drug product. Each study number should have a batch of drug product linked with it.

* A listing of the manufacturing procedure used for the different batches of drug substance.

* A listing of the characteristics (e.g., coating, scoring) for each of the batches of drug product.

Can you please specify where in the application this information can be found?

Thanks,

LCDR Lori Garcia, R.Ph.
Regulatory Project Manager
FDA CDER/OND/DPAP
Bldg. 22, Rm. 3343
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
Phone: (301) 796-1212
lori.garcia@fda.hhs.gov

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/s/

Lori Garcia
10/23/2006 04:58:50 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5 mg Tablets.

We also refer to your September 25, 2006, electronic mail communication containing a response to our refuse-to-file letter dated September 22, 2006.

We have reviewed the referenced material and find your proposal to amend the NDA with the submission of the required data within 30 days acceptable.

Therefore, this application is hereby filed under section 505(b) of the Act, effective as of September 23, 2006, in accordance with 21 CFR 314.101(a).

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
10/18/2006 10:07:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) for Xyzal (levocetirizine dihydrochloride) 5mg Tablets that was the subject of our September 22, 2006, refusal to file letter.

In response to your September 25, 2006, request for a meeting under 21 CFR 314.101(a), we scheduled a meeting for:

Date: October 24, 2006

Time: 2:00pm-3:00pm EST

Location: Teleconference

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
10/2/2006 03:09:15 PM
signed for Sandy Barnes

Garcia, Lori

From: Garcia, Lori
Sent: Tuesday, September 26, 2006 8:20 AM
To: Chowdhury, Badrul A; Gilbert McClain, Lydia I; Boucher, Robert
Subject: FW: NDA 22-064 - UCB response to filing decision
Attachments: ATT68605.rtf; NDA 22-064 UCB response to refuse-to-file.doc; emfalert.txt

FYI: Refuse to file/Levocetirizine

From: Susan.Tegtmeyer@ucb-group.com [mailto:Susan.Tegtmeyer@ucb-group.com]
Sent: Monday, September 25, 2006 5:52 PM
To: Garcia, Lori
Subject: NDA 22-064 - UCB response to filing decision

Dear Lori,

Please see the attached for our response to the levocetirizine NDA 22-064 refusal-to-file fax received on September 22, 2006. I will phone you tomorrow to discuss in more detail if you any questions regarding the proposal.

Regards,
Susan

Susan Tegtmeyer
Senior Regulatory Affairs Manager
UCB Pharma, Inc
Atlanta
ph 770-970-8654
email susan.tegtmeyer@ucb-group.com

<<NDA 22-064 UCB response to refuse-to-file.doc>>

Dear Lori,

Please see the attached for our response to the levocetirizine NDA 22-064 refusal-to-file fax received on September 22, 2006. I will phone you tomorrow to discuss in more detail if you any questions regarding the proposal.

Regards,
Susan

Susan Tegtmeyer
Senior Regulatory Affairs Manager
UCB Pharma, Inc
Atlanta
ph 770-970-8654
email susan.tegtmeyer@ucb-group.com

UCB response to the NDA 22-064 filing decision September 25, 2006

Reference is made to your correspondence received by fax September 22, 2006, indicating that a refuse-to-file decision has been made regarding the levocetirizine 5 mg tablet NDA 22-064, submitted July 24, 2006. This decision was reached due to the omission of an Integrated Summary of Efficacy (ISE), which is required under 21 CFR 314.50(d)(5)(v). As offered in your letter, we would like to request an informal conference, to be conducted by telephone at your earliest convenience, to discuss the refuse-to-file decision.

UCB discussed plans for the NDA at a Pre-IND Meeting held June 14, 2005. As was communicated in the Briefing Package submitted May 16, 2005 in support of that meeting, UCB clearly stated its intent not to include an ISE in Module 5, but rather to include a comprehensive summary of efficacy in the Module 2 (specifically, Module 2.7.3, Summary of Clinical Efficacy). Inclusion of a Module 5.3.5 ISE, while fulfilling a requirement under 21 CFR 314.50(d)(5)(v), would not have provided any information not already provided in the Module 2.7.3 Summary of Clinical Efficacy. In response to UCB's question regarding the planned presentation of clinical data, the Division affirmed that "Your planned presentation may be adequate for review." UCB intended to further discuss the plans for the NDA contents in a Pre-NDA meeting, requested March 15, 2006, however the Division declined to grant the meeting.

Following the 24 July 2006 submission of NDA 22-064 under Section 505(b)(2), we were contacted by the Division Project Manager on August 29, 2006 asking for the location of the ISE. The Project Manager was told that the ISE was not included in the NDA, that efficacy was addressed in the Module 2.7.3 Summary of Clinical Efficacy. That Summary of Efficacy contains all information that would otherwise have been included in an ISE. We had no further communication from the Division on this issue. Had we been aware that the omission of the ISE was not acceptable and was being considered as grounds for refusal-to-file, we would have worked to prepare an ISE for submission within the time remaining for a filing decision in order to complete the application.

We acknowledge that we may have misinterpreted the Division's response to our proposal regarding the omission of the ISE in the 505(b)(2) NDA for levocetirizine 5 mg tablets, and therefore we offer to provide the requested ISE within approximately 30 days. Since all other information is already contained in the application to allow for a substantive review, and the ISE will contain no new information, we would like to respectfully request reconsideration of the refusal-to-file decision regarding NDA 22-064, and ask that we be allowed to amend the NDA with the submission of an ISE. The ISE will be formatted as a stand-alone document for ease of review. This is the proposal that we wish to discuss with you at the informal teleconference.

UCB also acknowledges the request (not a refusal-to-file issue) for a reanalysis of studies A00266, A00268, A00303, A00304 and A00265 to omit ocular pruritus from the T4SS score. We will perform this reanalysis and submit the results to NDA 22-064 as soon as possible following submission of the ISE to NDA 22-064.

The requirement for submission of the SPL version of the draft labeling (not a refusal-to-file issue) is also mentioned in the September 22, 2006 correspondence. As previously

communicated to the Division, the submission of the SPL was delayed due to issues with the conversion to SNOMED terminology. Please note that the SPL version of the labeling was submitted as an amendment to NDA 22-064 on September 19, 2006.

The efficacy analysis datasets requested by the Division on August 14, 2006 are now available and as previously discussed with the Division Project Manager and Supervisory Project Manager, we had intended to submit these as an amendment to NDA 22-064 not later than September 27, 2006.

In closing, we hope that with the exception of the issues identified in your correspondence, that there are no other concerns identified during your screening of our NDA submission. UCB has endeavored to provide the Division with a quality submission that meets your expectations and we wish to continue to work collaboratively with the Division review team.

We look forward to the opportunity to discuss the resolution of this matter regarding the ISE with the Division.

MEMORANDUM

Date: October 11, 2006

From: Robert M. Boucher, MD, MPH
Medical Officer, Division of Pulmonary and Allergy Products
Through: Lydia Gilbert-McClain, MD
Clinical Team Leader, Division of Pulmonary and Allergy Products

To: NDA 22-064
Xyzal (levocetirizine dihydrochloride)
UCB, Inc.

Subject: Filing memorandum

The NDA 22-064 for Xyzal 5 mg tablets (levocetirizine dihydrochloride), submitted by UCB, Inc., under section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act was received by CDER July 25, 2006. The product, a H_1 receptor antagonist, is the R-enantiomer of the racemate cetirizine. The applicant seeks approval for the drug in the treatment of seasonal and perennial allergic rhinitis, and chronic idiopathic urticaria in patients six years of age and older.

After review, the Division sent a letter via fax to the applicant on September 22, 2006 stating that the application was insufficiently complete to permit a substantive review. The Division refused to file the application under 21 CFR 314.101(d) due to the absence of an Integrated Summary of Efficacy (ISE) as required under 21 CFR 314.50(d)(5)(v).

The applicant responded to the refuse-to-file decision in a letter dated September 25, 2006, in which they referenced the Briefing Package (submitted May 16, 2005) for a Pre-IND meeting held June 14, 2005. The applicant noted that within the Briefing Package it had stated its intent not to include an ISE, but, rather, a comprehensive summary of efficacy in Module 2. The applicant further stated that when UCB questioned the Division regarding UCB's planned presentation of the clinical data, the Division affirmed that "Your planned presentation may be adequate for review."

The clinical review team, which had made its refuse-to-file recommendation based upon the contents of the NDA, the Pre-IND-related clinical reviews, and associated meeting minutes, returned to the original Pre-IND Briefing Package, located the section referenced by the applicant, and found the applicant's claim to be substantially correct.

The Clinical Review team has reviewed the applicant's appeal of the refuse-to-file determination and believes the appeal is justified.

The Clinical review team recommends that the Division rescind the refuse to file action and file the NDA. The review issues remain, the most salient of which involves a re-analysis of data from several pivotal studies supporting efficacy claims.

Recommendation: The application is fileable.

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/s/

Robert M Boucher
10/11/2006 04:11:39 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5mg Tablets.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. You did not submit an Integrated Summary of Efficacy (ISE) as required under 21 CFR 314.50(d)(5)(v).

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

In addition, we have identified the following issues during our filing review of your NDA that are not refuse-to-file issues.

A. Your pivotal and supporting allergic rhinitis studies (A00266, A00268, A00303, A00304, A00265) used the T4SS, which included "ocular pruritus," to assess the primary efficacy outcome. However, the Division's recommended total nasal symptom

score (TNSS) does not include "ocular pruritus." Refer to the Agency's draft guidance for industry "Allergic Rhinitis: Clinical Development Programs for Drug Products."

Re-analyze the efficacy data for the studies A00266, A00268, A00303, A00304, and A00265 removing "ocular pruritus" from the total symptom score. Re-calculate the mean change from baseline using the revised total score (i.e., without the "ocular pruritus" symptom).

B. We note that SPL has not been submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. During the initial implementation phase of the PLR (until the end of 2006), FDA advises applicants to make a good faith effort to provide PLR-compliant SPL with their marketing applications or efficacy supplements. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

C. Please submit the completed Highlights Data Element Table with your SPL. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (http://www.fda.gov/oc/datacouncil) under Structured Product Labeling: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table". This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
9/22/2006 03:59:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

NDA ACKNOWLEDGMENT

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Xyzal (levocetirizine dihydrochloride) 5mg Tablets
Review Priority Classification:	Standard (S)
Date of Application:	July 24, 2006
Date of Receipt:	July 25, 2006
Our Reference Number:	NDA 22-064

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 23, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 25, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 796-1212.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
8/29/2006 04:43:46 PM
signed for Sandy Barnes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

INFORMATION REQUEST LETTER

UCB, Inc.
1950 Lake Park Drive
Smyrna, Georgia 30080

Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your July 24, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for levocetirizine dihydrochloride (Xyzal) 5mg Tablets.

We are reviewing the Statistical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide analysis datasets for Studies A217, A222, A00268, A00303 and A00306 for SAR, for Studies A219, A00264, A00265, A00266 and A00304 for PAR, and for Studies A00269 and A00270 for CIU. These datasets should contain Patient ID; investigative site; Country; treatment ID; covariates included in primary analysis, if any; age; gender; weight; baseline value and on-treatment value for all important primary and secondary efficacy analysis variables (i.e. weekly and global means for T4SS, weekly and global means of each symptom, etc.); and indicator flags for whether or not the patient was included in the ITT population, and whether or not included in the per protocol population.

2. It appears that diary card symptoms are contained in datasets DRCSYM or EFFDRR2. However, it is unclear whether these are just on-treatment symptom assessments or both baseline and on-treatment assessments. If these datasets include only on-treatment assessments, provide the location of the baseline symptom assessments. If you have not provided the baseline assessments, provide datasets containing them. If these data sets contain both baseline and on-treatment assessments, indicate how the baseline assessments and on-treatment assessments can be distinguished.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at 301-796-1212.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
8/14/2006 11:00:47 AM
signed for Sandy Barnes

UCB, Inc. – 1950 Lake Park Drive – Smyrna, Georgia 30080

24 July 2006

Badrul Chowdhury M.D. Ph.D
Director, Division of Pulmonary and Allergy Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-064
Xyzal® (levocetirizine dihydrochloride) 5 mg tablets
ORIGINAL SUBMISSION

Dear Dr. Chowdhury,

Pursuant to 21 CFR 314.50 and Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act, UCB, Inc., hereby submits an original New Drug Application (NDA) for approval to market levocetirizine dihydrochloride 5 mg oral tablets as a prescription product for the symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in adults and children 6 years of age and older. This product is not the subject of a US IND; previous correspondence has been submitted under P-IND 72,233.

Levocetirizine dihydrochloride, an oral H_1-histamine receptor antagonist, is the R-enantiomer of the approved racemate cetirizine and has been found to be solely responsible for the therapeutic antihistaminic activity of cetirizine and has no anticholinergic and serotonergic activity. This 505(b)(2) NDA references the approved prescription drug Zyrtec® (cetirizine hydrochloride) which is the subject of the following NDAs sponsored by Pfizer: NDA 19-835 (5 mg and 10 mg tablets), NDA 20-346 (oral syrup, 5 mg/mL) and NDA 21-621 (chewable tablets, 5 mg and 10 mg).

The NDA is provided in accordance with the January 1999 "Guidance for Industry: Providing Submissions in Electronic Format – NDAs" and the October 2003 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations".

The structure of this electronic NDA is a Common Technical Document (CTD) hybrid provided as NDA items. Each item is composed of CTD elements. In addition to the Table of Contents for the NDA items (ndatoc.pdf), a CTD map (cdtmap.pdf) is provided to map the CTD elements to the NDA items. Module 1 elements (administrative documents) are provided in both paper and electronic format.

The draft levocetirizine labeling is provided in accordance with the Physician Labeling Rule which became effective 30 June 2006. A version of the draft labeling has also been provided in the format following the 1979 labeling regulations. This version is included to facilitate the review of the draft levocetirizine labeling in relation to the current approved labeling of the reference drug cetirizine. Due to technical issues regarding the conversion to the

Structured Product Labeling (SPL) for the draft Physician Labeling Rule (PLR) version of the labeling, and the unavailability of the appropriate tools for conversion of MedDRA coding to the newly required SNOMED coding, UCB is submitting the PLR format as a pdf document with MedDRA coding. UCB is working with SPL specialists at FDA to convert the PLR labeling to SPL format. UCB will submit an SPL/MedDRA version of the draft PLR as soon as possible, and will work with the FDA to prepare an SPL/SNOMED version of the labeling as the appropriate conversion tools become available.

UCB submitted a request for review of the proposed proprietary name Xyzal® (and _____ as a backup option) to P-IND 72,233 on 06 October 2005. To date, UCB has not received FDA's preliminary assessment regarding the suitability of the proprietary names. A copy of the proprietary name review request is provided in this application.

UCB met with the Division on 14 June 2005 to review the levocetirizine development plan and the general plan to submit a 505(b)(2) NDA for levocetirizine. These development and submission plans also were also the subject of a teleconference held on 28 October 2005 with the Division, addressing data demonstrating pharmacokinetic equivalence and pharmacodynamic clinical comparability between levocetirizine and cetirizine to support approval of levocetirizine. Recognizing the importance that the Division attributes to this data relative to the ultimate potential approvability of levocetirizine, UCB implemented the Division's specific guidance in this regard and conducted the type of study recommended as most appropriate by the Division, i.e., a clinical efficacy study (EEU design) comparing two doses of levocetirizine to two doses of cetirizine (A00412).

As proposed in the 14 June 2005 meeting package, the NDA includes full clinical study reports for those studies which support the draft labeling or which include the reference drug cetirizine as a comparator. Synopses from full reports are included for other studies, and progress reports are included for studies on-going at the cut-off date of 31 March 2006. Ongoing studies and studies initiated after the clinical cut-off date will be addressed in the 120-Day Safety Update.

Case Report Forms are included for all completed studies in which serious adverse events or withdrawals due to adverse events occurred. In the briefing package for the 14 June 2005 meeting, UCB had proposed that no Case Report Tabulations (CRTs) would be included in this NDA. Although the Division did not indicate that this was unacceptable, UCB has chosen to include CRTs for 20 of the clinical studies which may be considered most meaningful in the review of this NDA.

Module 5 includes an Integrated Summary of Safety (ISS). The ISS reviews safety data pooled up to the cut-off date of 15 August 2005, and unpooled data up to a cut-off date of 31 March 2006. Post-marketing safety adverse events are also reviewed in this submission.

A justification for prescription status for levocetirizine, as requested by the Division, is included in Module 2.2 CTD Introduction.

UCB is requesting a deferral for the submission of data supporting the use of levocetirizine in the pediatric population below 6 years of age. [redacted]

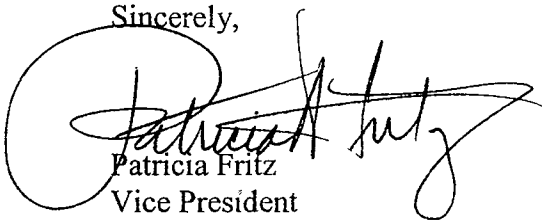
All electronic elements of the submission have been scanned for possible viruses using McAfee Virus Scan for Windows, Version 7.1.

The use fee I.D. number for this application is PD3006593. The user fee was submitted by wire transfer on 14 July 2006. The Form FDA 3397 and the wire transfer receipt are included.

Any questions regarding this application can be directed to the following contact person:
Susan Tegtmeyer, M.S.
Manager, Regulatory Affairs
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080
Telephone: 770-970-8654
Facsimile: 770-970-8345
Email: susan.tegtmeyer@ucb-group.com

Should there be any questions, please do not hesitate to contact us.

Sincerely,



Patricia Fritz
Vice President
Global Regulatory Affairs
UCB, Inc.

Desk Copy:

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

UCB PHARMA INC
Crystal Ross
1950 Lake Park Drive
Smyrna GA 30080
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-064

2. TELEPHONE NUMBER
770-970-8736

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Levocetirizine Dihydrochloride

6. USER FEE I.D. NUMBER
PD3006593

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Patricia N Tutt	V.P. Global Reg. Affairs	12 July 06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
UCB, Inc	07/24/2006
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
770-970-7500	770-970-8345
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1950 Lake Park Drive Smyrna, GA 30080	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE UCB, Inc. 1950 Lake Park Drive Smyrna, GA 300080

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 22-064

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
levocetirizine dihydrochloride	Xyzal

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
levocetirizine dihydrochloride		ucb 28556
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
tablet	5 mg	oral

(PROPOSED) INDICATION(S) FOR USE:
seasonal allergic rhinitis, perennial allergic rhinitis, chronic idiopathic urticaria

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Zyrtec (cetirizine hydrochloride) Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original NDA

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Module 3.2.P.3. Sites are ready for inspection.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

PIND 72,233
DMFs _____

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Patricia Fritz Vice President, Global Regulatory Affairs	07/24/2006

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1950 Lake Park Drive, Smyrna, GA 30080	(770) 970-8585

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NDA Pharmacology Fileability Check List

NDA No: 22-064

Date of submission: 7/24/06

Date of Fileability meeting: 9/12/06

Information to Sponsor: Yes ( ) No (X)

Date of check list: 9/19/06

(1) On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review? Yes (X) No ( ) NA ( ).

(2) On its face, is the Pharm/Tox section of the NDA legible for review?
Yes (X) No ( ) NA ( ).

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Yes (X) No ( ) NA ( )

	Yes	No	NA
Pharmacology	(X)	( )	( )
ADME	(X)	( )	( )
Toxicology (duration, route of administration and species specified)			
acute	(X)	( )	( )
subchronic and chronic studies	(X)	( )	( )
reproductive studies	(X)	( )	( )
carcinogenicity studies	(X)	( )	( )
mutagenicity studies	(X)	( )	( )
special studies	( )	( )	(X)
others	( )	( )	(X)

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes ( ) No ( ) NA (X)

If yes, has the applicant made an appropriate effort to repeat the studies using the to be marketed product, to bridge the studies or to explain why such repetition or bridging should not be required? Yes ( ) No ( ) NA ( ).

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57? Yes (X) No ( ).

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes (X) No ( ) NA ( )

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes (X) No ( ) NA ( )

If not, has the applicant submitted a rationale to justify the alternative route?
Yes ( ) No ( ) NA ( )

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes (X) No ( ) NA ( )

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes ( ) No ( ) NA (X)

However, there are impurities/degradant issues which may require qualification.

(10) Are there any outstanding preclinical issues? Yes ( ) No (X)

(11) From a preclinical perspective, is this NDA fileable? Yes (X) No ( ).
If no, state below why it is not.

(12) Should any additional information/data be requested? Yes ( ) No (X)

NDA Planning Timeline

NDA No.: 22-064

Date of planning timeline:	9/11/06
PDUFA Due Date:	5/25/07
Projected review completion date:	3/25/07

	Milestone Dates
Pharmacology and ADME	3/25/07
Toxicology	3/25/07
General toxicity studies	
Carcinogenicity studies and mutagenicity studies	
Reproductive studies	
Special studies and others	
Labeling	3/25/07

Signatures (optional):

Reviewer Signature _____
Lawrence F. Sancilio, Ph.D.

Supervisor Signature _____
C. Joseph Sun, Ph.D.

Concurrence Yes ___ **No** ___

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/s/

Lawrence Sancilio
9/19/2006 03:49:56 PM
PHARMACOLOGIST

Joseph Sun
9/19/2006 03:58:27 PM
PHARMACOLOGIST
I concur.

MEETING MINUTES

APPLICATION: PIND 72,233
SPONSOR: UCB Pharma, Inc.
DRUG NAME: levocetirizine dihydrochloride
DATE: October 31, 2005

UCB Pharma Representatives:
Catherine Arendt, M.D., Clinical Research
Remy von Frenckell, Ph.D., Biostatistics
Patty Fritz, Vice President, Regulatory Affairs
Susan Tegtmeyer, Manager, Regulatory Affairs

Division of Pulmonary & Allergy Products Representatives:
Badrul A. Chowdhury, M.D., Ph.D., Director
Eugene J. Sullivan, M.D., FCCP, Deputy Director
Peter Starke, M.D., Clinical Team Leader
Warner Carr, M.D., Clinical Reviewer
Ching-Long J. Sun, Ph.D., Supervisory Pharmacology/Toxicology
Lawrence F. Sancilio, Ph.D., Pharmacology/Toxicology Reviewer
James R. Gebert, Ph.D., Acting Biometrics Team Leader
Feng Zhou, M.S., Biometrics Reviewer
Emmanuel O. Fadiran, Rh.P., Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Carol F. Hill, M.S., Regulatory Project Manager

Reference is made to the meeting held between representatives of your company and the Division of Pulmonary and Allergy Products on October 31, 2005. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 796-1226.

Background:
UCB Pharma submitted a type B meeting request dated September 1, 2005, to discuss the development and submission plan for levocetirizine dihydrochloride for [redacted] UCB Pharma also submitted a briefing package dated September 29, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the division responded to UCB Pharma's questions via fax on October 27, 2005. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. UCB Pharma's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4

Drafted: CHill/November 7, 2005

Initialed: EFadiran/November 17, 2005
FZhou/November 8, 2005
JGebert/November 8, 2005
LSancilio/November 8, 2005
CSun/November 8, 2005
WCarr/November 16, 2005
PStarke/November 16, 2005
ESullivan/November 22, 2005
BChowdhury/November 28, 2005

Finalized: CHill/November 29, 2005

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/s/

Carol F. Hill
11/29/2005 02:30:36 PM

MEMORANDUM OF TELECONFERENCE MINUTES

DATE: October 28, 2005

TIME: 12:30 PM

LOCATION: Conference Room 3376

APPLICATION: Pre IND 72, 233 levocetirizine Submission No. 003

FDA Representatives:

Warner Carr, M.D., Medical Officer
Badrul Chowdhury, M.D., Ph.D., Division Director
Ruthanna Davi, Biostatistics Team Leader
Anthony Zeccola, Regulatory Management Officer
Feng Zhou, Biostatistics Review

UCB Pharma, Inc. Representatives:

Catherine Arendt, Clinical Research
Patty Fritz, Regulatory Affairs
Susan Tegtmeyer, Regulatory Affairs
Remy von Frenckell, Biostatistics

Background

Teleconference to convey comment in response to September 30, 2005 submission to Pre IND 72,233 number 003.

Discussion

While we note your extensive development program, we expect demonstration of pharmacokinetic (PK) equivalence and pharmacodynamic (PD) clinical comparability between levocetirizine and cetirizine to support approval of levocetirizine. Whether you have adequate PK and PD data or not will be a review issue. You should submit this data at the time of your application and provide justification why it supports the approval of levocetirizine for the proposed indications. Based on preliminary review of your submission you may not have adequate data because the clinical program lacks a clinical efficacy study in which two doses of levocetirizine have been compared to two doses of cetirizine in the same study.

We suggest that you consider conducting a study which will allow for a better assessment of efficacy comparability of the two drugs. Examples include a traditional 2-week

outpatient study, or in a day- in-the park type of study, or in an EEU study. The EEU study is probably most appropriate, because the design may allow for demonstration of some dose-response of the two drugs, which will allow for a better assessment of efficacy comparability of the two drugs. The Division considers EEU study as an appropriate PD study for this purpose.

The Sponsor asked whether 2 studies would be acceptable. Dr. Chowdhury responded that cross-study comparison is generally not a valid strategy. Dr. Chowdhury further stated that if the company feels that they have adequate data to address the concern raised, they may submit it to the NDA. The Division, based on preliminary review of the program, has discomfort with this the plan of cross-study comparison.

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/s/

Anthony Zeccola
10/28/2005 01:53:17 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 14, 2005
TIME: 1:00pm-2:30pm
APPLICATION: PIND 72,233
DRUG NAME: Levocetirizine
TYPE OF MEETING: Pre-IND (Type B)

MEETING RECORDER: Lori Garcia, R.Ph.

FDA ATTENDEES:

Division of Pulmonary and Allergy Drug Products
Badrul A. Chowdhury, M.D., Ph.D., Division Director
Peter Starke, M.D., Clinical Team Leader
Warner Carr, M.D., Clinical Reviewer
Joe Sun, Ph.D., Pharmacology/Toxicology Team Leader
Larry Sancilio, Ph.D., Pharmacology/Toxicology Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Sayed Al Habet, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
Steve Wilson, Ph.D., Acting Biostatistics Team Leader
Feng Zhou, Ph.D., Biostatistics Reviewer
Jean Nashed, Ph.D., Chemistry Reviewer
Rik Lostritto, Ph.D., Chemistry Team Leader
Lori Garcia, R.Ph., Regulatory Project Manager
Eric Duffy, Ph.D., Division Director, DNDC II
Ying Wang, Ph.D., Chemistry Reviewer, Manufacturing Sciences, ONDC
Christine Moore, Ph.D., Branch Chief, Manufacturing Sciences, ONDC

EXTERNAL CONSTITUENT ATTENDEES:

UCB Pharma, Inc.
Patty Fritz - Regulatory Affairs
Susan Tegtmeyer - Regulatory Affairs
Mary Alonso - CMC Regulatory Affairs
Catherine Arendt - Clinical Research
Anne Danniau – Biostatistics
Remy Von Frenckell – Biostatistics
Margherita Strolin-Benedetti – Biopharmaceutics
Marie-Etienne Pinelli – Clinical Development

BACKGROUND:

UCB Pharma, Inc., submitted a Type B (pre-IND) meeting request dated April 14, 2005, for the purpose of discussing UCB's plan to submit a 505(b)(2) NDA for levocetirizine, referencing the listed drug cetirizine hydrochloride (Zyrtec®).

UCB Pharma, Inc. also submitted a briefing package dated May 16, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the division responded to these questions via fax on June 13, 2005. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. UCB's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

MEETING OBJECTIVES:

To further clarify and discuss the responses faxed to UCB Pharma, Inc. on June 13, 2005, by the Division.

QUESTIONS AND DISCUSSION:

QUESTION 1: 505(B)(2) NDA SUBMISSION STRATEGY

Does the division agree that NDA submission under the provisions of 505(b)(2), referencing the Division's previous findings of safety and effectiveness for racemic cetirizine, is appropriate for levocetirizine?

FDA RESPONSE:

1. *Yes, we agree that a NDA submission under the provisions of 505(b)(2) may be appropriate for levocetirizine.*

2. *A 505(b)(2) should include all of the elements described in the Guidance for Industry: Applications Covered by Section 505(b)(2).*

3. *Clarify what portions of the reference product application you will rely on for your 505(b)(2).*

QUESTION 2: 505(B)(2) NDA DATA PRESENTATION (NONCLINICAL)

Does the Division agree with the proposed presentation of levocetirizine nonclinical data in the planned 505(b)(2) NDA?

FDA RESPONSE:

Yes, we agree since the results of two 13-week bridging studies in rats and dogs and teratology studies in rats and rabbits will be submitted. If the toxicity profiles between levocetirizine and cetirizine are different, further studies may be required. Furthermore, to claim that levocetirizine is less toxic than cetirizine based on the results of the 13-week studies, may require you to conduct additional studies.

Note: The levocetirizine used in the pre-clinical and clinical studies was synthesized by different methods. If the impurity profile is different, qualification is required for each impurity in the clinical batch that exceeds the qualification threshold (see ADDITIONAL COMMENTS (CMC) section).

QUESTION 3: 505(B)(2) NDA DATA PRESENTATION (CLINICAL)

Does the Division agree that the planned presentation of levocetirizine clinical data in the planned 505(b)(2) NDA is appropriate and adequate to support the Division's review of Levocetirizine?

FDA RESPONSE:

1. *Your planned presentation may be adequate for review.*

2. *The clinical program is expected to demonstrate and support equal exposure and pharmacodynamic efficacy from levocetirizine 2.5 mg & 5 mg, compared to cetirizine 5 mg & 10 mg, respectively. This would be ideally demonstrated by showing PK equivalence in a clinical pharmacology study, and PD similarity in a dose ranging efficacy study using at least 2 different doses of levocetirizine and cetirizine in the same study.*

DISCUSSION:

UCB noted that they have conducted nine adequate and well controlled studies to demonstrate the safety and efficacy of levocetirizine in adults with allergic rhinitis. Three of these studies demonstrated that both 2.5 mg and 5 mg levocetirizine were statistically significantly superior to placebo. The remaining six studies only studied a dose of 5 mg levocetirizine and demonstrated statistical superiority to placebo.

Per UCB, four additional studies (A184, A190, A379 and A380) were conducted specifically to evaluate the pharmacodynamic efficacy of levocetirizine as compared to cetirizine. These four studies utilized wheal and flare, nasal provocation, EEU chamber and thermography as models of pharmacodynamic efficacy, respectively, and provide comparisons of levocetirizine 2.5 mg and cetirizine 5 mg and levocetirizine 5 mg and cetirizine 10 mg, albeit not in the same study.

UCB noted that the equivalency of levocetirizine 2.5 mg and cetirizine 5 mg was demonstrated in the wheal and flare, Study A184. In Studies A190, A379 and A380 pharmacodynamic efficacy was also demonstrated to be equal when comparing levocetirizine 5 mg to cetirizine 10 mg.

Additionally, UCB noted that Study A221 included pharmacokinetic analyses comparing levocetirizine 10 mg and cetirizine 20 mg. The doses were selected based on the sensitivity of the chiral assay method at the time the study was conducted (1996).

Pharmacodynamic Studies			
Study	Design/PD Model	Levocetirizine	Cetirizine
A184	Histamine induced wheal/flare; db, crossover, in healthy volunteers, comparing levocetirizine, cetirizine and dextrocetirizine	2.5 mg	5 mg
A190	Nasal provocation; db, crossover, in healthy volunteers comparing levocetirizine, cetirizine, dextrocetirizine and placebo	5 mg	10 mg
A379	EEU Chamber; db, parallel group, comparison of levocetirizine, cetirizine and placebo	5 mg	10 mg
A380	PD thermography; db, crossover comparing levocetirizine, cetirizine and placebo	5 mg	10 mg

UCB considers that the equivalency of the pharmacodynamic efficacy of levocetirizine 2.5 and 5 mg, as compared to cetirizine 5 mg and 10 mg has been demonstrated. UCB proposed to perform a pharmacokinetic study in healthy volunteers comparing single doses of levocetirizine 2.5 mg and 5 mg and cetirizine 5 and 10 mg to fulfill the FDA's request, and requested confirmation that this approach would be found acceptable.

The Division noted that they recognize UCB's extensive development program and stated that we have an expectation that pharmacokinetic (PK) equivalence and pharmacodynamic clinical comparability between lecovetirizine and cetirizine be demonstrated to support approval of levocetirizine. Whether or not UCB has met this challenge in their development program will be a review issue. Based on UCB's submission, it appears that PK equivalence has been demonstrated. The Division pointed out that the clinical program may not be adequate to support comparability of the two drugs because the program lacks a clinical efficacy study in which two doses of levocetirizine have been compared to two doses of cetirizine in the same study. The Division notes that UCB has conducted various PD studies, such as histamine challenge study, nasal provocation study, EEU chamber and thermography studies. The Division pointed out that these studies generally do not correlate with clinical efficacy and may not form the basis for demonstrating clinical comparability or efficacy claims. The Division pointed out to UCB that the product label of many US marketed antihistamines describes

such studies with added statements that clinical relevance of these study findings is unknown. The Division expects clinical comparability between levocetirizine and cetirizine be demonstrated in a clinically relevant study, such as either in a traditional 2-week outpatient study, or in a day-in-the park type of study, or in an EEU study. The EEU study is probably most appropriate, because the design may allow for demonstration of some dose-response of the two drugs, which will allow for a better assessment of efficacy comparability of the two drugs. The Division considers EEU study as an appropriate PD study for this purpose. The Division noted that UCB may already have the sufficient data from multiple studies to support similarity of levocetirizine to cetirizine, however, this would be a review issue. The Division asked UCB to consider the Division's expectations and review the studies that they have conducted and decide if they would need to conduct a pharmacodynamic efficacy study, such as an EEU study. The Division acknowledged that it is possible that the existing database may be adequate to support similarity of the two drugs.

The Division stated that if Study A221 demonstrated bioequivalence (BE) between levocetirizine 10 mg and cetirizine 20 mg, the sponsor may not need to conduct another BE study using lower doses of the formulations, but rather provide justification for using the higher doses. The Division further stated that the requirement for a BE study with the 2.5mg dose could be waived if the F2>50% for the comparison of the *in vitro* dissolution profiles. UCB noted that the F2 was not calculated because the formulations were rapidly dissolved (>85% dissolved in 10 minutes). The Division agreed that no F2 calculation would be needed in this case, and requested that UCB provide justification for the request for the waiver of the BE study with the 2.5mg tablet formulation.

Does the Division agree with the proposed levocetirizine safety data analysis described in the Outline of Statistical Analysis Plan (vol.1, pg. 82) for the planned Integrated Summary of Safety?

FDA RESPONSE:

Your proposed safety data analysis seems reasonable.

Is the plan for the submission of CRFs and Analysis Datasets (vol. 1, pg 117) acceptable to the Division? Is the submission of the analysis datasets for the ISS adequate for the review of this 505(b)(2) NDA? Are the datasets submitted in electronic format as SAS transport files acceptable for the archival copy of the NDA?

FDA RESPONSE:

1. *Your plan for submission of CRFs and Analysis seems acceptable. Include a CRF for those subjects who experienced an SAE, death or discontinuation due to adverse event in any clinical trial.*

2. *The submission of PK data as SAS transport files is acceptable. You are encouraged to submit PK and individual concentration data as SAS transport files.*

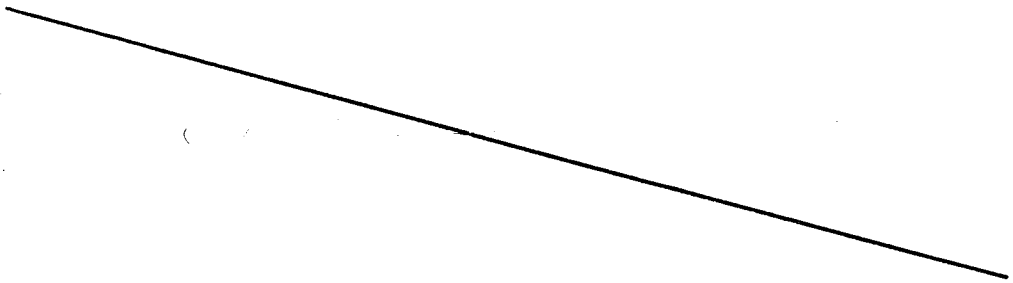
QUESTION 4 : PEDIATRIC INDICATION

Does the Division agree that, based on the availability of pediatric data for levocetirizine and the FDA's previous findings of safety and effectiveness of racemic cetirizine in the pediatric population, no additional pediatric clinical data are required

---

FDA RESPONSE:

1. *Based on your submission, you appear to have adequate data and reasoning to support an application down to the age of 6 years.*



DISCUSSION:

Based on the Division's response, UCB stated that they will seek a deferral for pediatric patients under 6 years of age.

The Division stated that UCB's plan is acceptable.

QUESTION 5: CHRONIC IDIOPATHIC URTICARIA INDICATION

Does the Division agree that under a 505(b)(2) provisions, UCB is not required to pursue all indications currently approved for the referenced listed drug? Does the Division agree with UCB's plans to include safety data from the CIU studies in the Integrated Summary of Safety, and to submit synopses only of the CIU clinical studies if the NDA if the indication is not pursued?

FDA RESPONSE:

Under the provisions of 505(b), you are not required to pursue all indications. However, your rationale for not pursuing all indications currently approved for cetirizine is not clear. It appears that you may have scientific reasoning and data to support all of the indications for which cetirizine is approved. In the interest of public health, it would seem appropriate that your NDA for levocetirizine seek approval for all indications currently approved for cetirizine.

QUESTION 6: PERSISTENT ALLERGIC RHINITIS

UCB would appreciate feedback regarding the FDA's views on the ARIA classification of allergic rhinitis as "intermittent" and "persistent".

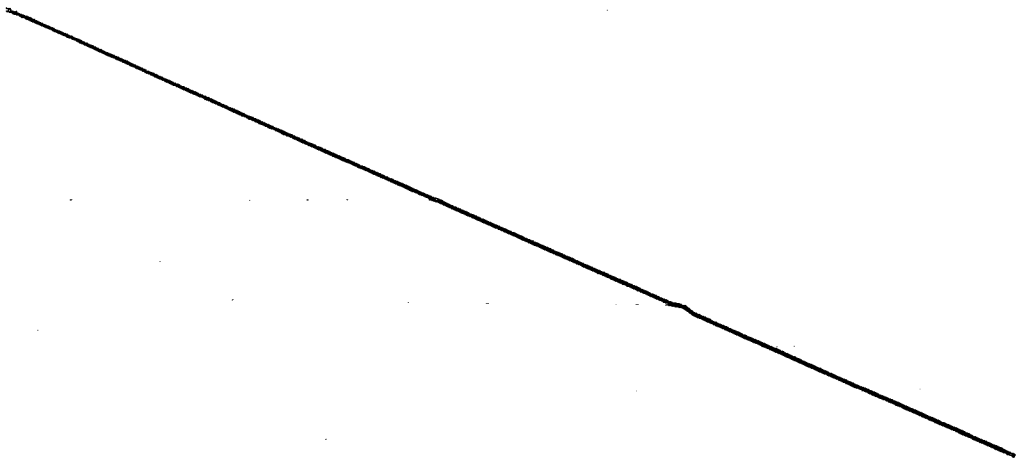
FDA RESPONSE:

The Division does not view allergic rhinitis as intermittent and persistent. For the purposes of drug development, allergic rhinitis has been classified as seasonal or perennial. We refer you to the Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products.

QUESTION 7: DRUG SUBSTANCE EQUIVALENCE

Does the Division agree that the approach to establish equivalence between the levocetirizine produced

FDA RESPONSE:



Assuming the equivalency of the drug substance upon the CMC review, the proposed approach is acceptable from clinical pharmacology & biopharmaceutics perspectives.

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 5

The Division stated that UCB's approach seems reasonable based on the information that we have, but ultimately, it will be a review issue.

The Division asked if UCB plans to submit a full CMC preNDA package, and UCB confirmed that that is their plan. The Division, referring to the *Guidance for Review Staff and Industry, Good Review Management Principles and Practices for PDUFA Products*, reminded UCB that a full and complete NDA is expected at the time of submission, including the complete set of the stability data.

There were no further questions at this point, and the meeting was concluded at approximately 1:50pm.

Lori Garcia, R.Ph., Regulatory Project Manager

Drafted : LGarcia/June 14, 2005

Initialed : JNashed/June 29, 2005
RLostritto/June 29, 2005
TFadiran/July 1, 2005
WCarr/June 29, 2005
BChowdhury/June 29, 2005

Finalized : LGarcia/July 1, 2005

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/s/

Lori Garcia
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