CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-064

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

PATENT CERTIFICATION

In the opinion and to the best knowledge of UCB, Inc., there are no patents, other than patents owned by UCB, Belgium, that claim the referenced listed drug or any other drug on which investigations relied upon for approval of this application were conducted by or for someone other than applicant, or that claim a use of such drugs for which applicant is seeking approval under this subsection.

Patricia A Fritz
Vice President, Global Regulatory Affairs

(770) 970-7500

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-064

NAME OF APPLICANT / NDA HOLDER
UCB, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Xyzal

ACTIVE INGREDIENT(S)	STRENGTH(S)
Levocetirizine Dihydrochloride	5 mg

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. Patent No. 5,698,558	Dec. 16, 1997	Dec. 16, 2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Sepracor, Inc.	84 Waterford Dr.	
	City/State: Marlborough, MA	
	ZIP Code: 01752	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1-10	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of seasonal allergic rhinitis due to allergens and/or perennial allergic rhinitis due to allergens according to proposed labeling.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
R J Paris.	7/21/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: RICHARD J. PARIS, JR., ATTORNEY FOR UCB, INC.

Address	City/State
1950 LAKE PARK DRIVE	SMYRNA, GA
ZIP Code	**Telephone Number**
30080	770-970-7500
FAX Number *(if available)*	**E-Mail Address *(if available)***

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

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TRADE NAME (OR PROPOSED TRADE NAME)
Xyzal

ACTIVE INGREDIENT(S)	STRENGTH(S)
Levocetirizine Dihydrochloride	5 mg

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This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. Patent No. 4,525,358	June 25, 1985	June 25, 2007

d. Name of Patent Owner	Address *(of Patent Owner)*	
UCB, Inc.	1950 Lake Park Drive	
	City/State: Smyrna, GA	
	ZIP Code: 30080	FAX Number *(if available)*
	Telephone Number: 770-970-7500	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☒ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**

The patent claims the form of the active ingredient that is descirbed in the pending NDA, among others, and is submitted for listing on that basis. Accordingly, no further testing is required.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
23-31	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of seasonal allergic rhinitis due to allergens, perennial allergic rhinitis due to allergens, and/or treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria according to proposed labeling.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

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RJ Paris.	7/21/06

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☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: RICHARD J. PARIS, JR., ATTORNEY FOR UCB, INC.	
Address: 1950 LAKE PARK DRIVE	City/State: SMYRNA, GA
ZIP Code: 30080	Telephone Number: 770-970-7500
FAX Number *(if available)*	E-Mail Address *(if available)*

PSC Media Arts (301) 443-1090 EF

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

STATEMENT OF CLAIMED EXCLUSIVITY

UCB, Inc. is claiming 5 years exclusivity for levocetirizine dihydrochloride 5 mg tablets (NDA 22-064) under 21 CFR 314.(50)(j)(3) for the relief of symptoms associated with seasonal allergic rhinitis, perennial allergic rhinitis, and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

This new drug application contains new clinical investigations that are essential to approval of the application and were conducted or sponsored by UCB. To applicant's knowledge and belief, while a drug product containing the cetirizine racemate moiety has been approved previously, no drug product containing the single-enantiomer levocetirizine moiety has been approved previously.

Patricia A. Fritz
Vice President, Global Regulatory Affairs
UCB, Inc.

(770) 970-7500

EXCLUSIVITY SUMMARY

NDA # 22-064 SUPPL # HFD # 570

Trade Name Xyzal 5mg Tablet

Generic Name levocetirizine dihydrochloride

Applicant Name UCB

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-835 Zyrtec Tablets

NDA# 20-346 Zyrtec Liquid

NDA# 21-621 Zyrtec Chewable Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A217, A00266, A00268, A00264, A00269, A00270, A00303, A00304

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A217, A00266, A00268, A00264, A00269, A00270, A00303, A00304

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☒	! NO ☐
Explain:	! Explain:
The applicant states that the new	

clinical investigations that are essential to the approval of this application were conducted or sponsored by them.

Investigation #2	
YES ☒	NO ☐
Explain: The applicant states that the new clinical investigations that are essential to the approval of this application were conducted or sponsored by them.	Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Lori Garcia, RPh
Title: Regulatory Project Manager
Date: 5/21/07

Name of Office/Division Director signing form: Badrul A. Chowdhury, MD, PhD
Title: Division Director/DPAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Badrul Chowdhury
5/25/2007 05:30:52 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-064 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 7/25/06 **PDUFA Goal Date:** 5/25/07

HFD 570 **Trade and generic names/dosage form:** Xyzal (levocetirizine) 5mg

Applicant: UCB Pharma **Therapeutic Class:** _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☒ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indication #1: The relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☒ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply:** x **Partial Waiver** x **Deferred** ____ **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.__0___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.___<2_ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **xxDisease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__2___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__<6___ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **XX Adult studies ready for approval**
- ☐ **XX Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 5/31/09

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lori Garcia, R.Ph., Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: the relief of symptoms associated with perennial allergic rhinitis in adults and children 6 years of age and older.

Is this an orphan indication?

☐ **Yes. PREA does not apply. Skip to signature block.**

☒ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☒ **No: Please check all that apply: ____Partial Waiver __x__Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** <6	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **XX Adult studies ready for approval**
- ☐ **XX Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): 5/31/09

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

This page was completed by:

{See appended electronic signature page}

Lori Garcia, R.Ph., Project Manager

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

/s/

Lori Garcia
5/25/2007 05:38:36 PM

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

DEBARMENT CERTIFICATION STATEMENT

UCB, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

09-July-2006

Aaron Bartlone
Vice President, Global Preclinical/Clinical Quality Assurance

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
see attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Catherine Arendt, MD, Pharm D	Vice President, Clinical Development
FIRM / ORGANIZATION: UCB Inc	
SIGNATURE	DATE

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06)

PSC Graphics (301) 443-1090 EF

MEMORANDUM OF EMAIL COMMUNICATION

DATE: May 24, 2007

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: Additional information from UCB was requested via email on 5/23/07. The following emails provide regulatory counsel's response to UCB's submission and subsequent notification of acceptability to UCB.

Lori Garcia, R.Ph.
Regulatory Project Manager

MEMORANDUM OF E-MAIL COMMUNICATION

DATE: May 24, 2007

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: Emails denoting agreed-upon labeling revisions.

_____

Lori Garcia, R.Ph.
Regulatory Project Manager

Subject: NDA 22-064/label
Importance: High

Hi Susan,

We are reviewing the label you sent via email on 5/22/07, and we have a couple of comments. The Director will be looking at the label this evening, so it is possible that additional comments may be forthcoming, but we thought you might want to get started on recalculating the CI for the tables.

1." In tables 3 and 5 in the Clinical trial section" the —— CI is shown for the seasonal allergic rhinitis trial and the chronic Idiopathic Urticaria dose-ranging trial. We acknowledge that the ——— CI was used for these 2 studies however, the CI should be expressed as the 95% CI for all the studies. Recalculate the 95% CI for these 2 studies and put those numbers in the tables instead of the ←— CI numbers."

2. In the clinical trials section paragraph 2 in the second sentence " Efficacy was assessed using a total symptoms core from patient recording of 4 symptoms (sneezing.....) in ——— studies.....;" change ———— to five studies.

Thanks,

LACER Lori Garcia, Rap.
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

Email #1

From: Weiner, Janice
Sent: Tuesday, May 22, 2007 5:44 PM
To: Garcia, Lori
Cc: Colangelo, Kim M; Bernstein, Michael; Boocker, Nancy; Dickinson, Elizabeth; Dettelbach, Kim
Subject: FW: 5/25/07 goal date: [Xyzal] NDA 22-064 patent certification information

Lori,

In follow up to our telephone conversation, set forth below are the issues that should be addressed by the sponsor with respect to the patent certification information. These comments reflect Michael Bernstein's helpful input.

1. In general, it is unclear from UCB's correspondence who owns the '358 and '533 patents and the relationship between the UCB entity that submitted the 505(b)(2) application and the UCB entity(ies) that own the listed patents.

2. It had been my understanding that UCB represented to the Division that UCB (or a related corporate entity) was the owner of the '358 and '533 patents, yet they have only provided a letter (consenting to an immediate effective date of approval of NDA 22-064 and waiving the 45-day period described in 21 USC 355(c)(3)(C)) with respect to the '533 patent. Please ask UCB to clarify who owns the '358 patent and, if it is a UCB corporate entity, the relationship between the patent owner and the UCB entity that submitted the 505(b)(2) application for Xyzal. If the sponsor of the Xyzal 505(b)(2) application is the same corporate entity as the owner of the '358 patent, then they should clarify this in writing. If they are related corporate entities, then we do require notice of a paragraph IV certification and compliance with applicable regulatory requirements.

3. The letter from Pfizer confirms that Pfizer, Inc. owns the '533 and '358 patents. Again, it had been my understanding that UCB represented to the Division that UCB (or a related corporate entity) was the owner of the '358 and '533 patents. Please ask UCB to clarify, in writing, who owns or co-owns these patents. If Pfizer is not a patent owner, please ask UCB to advise as to Pfizer's interest in the patent (e.g., is Pfizer a licensee?). Under the circumstances, we would consider a written statement from UCB to be acceptable.

4. It is worth noting that if the sponsor does make any further submissions or amended submissions, they should ensure that all correspondence is dated, includes documentation of receipt of notice of the paragraph IV certification (per 21 CFR 314.52(e)), complies with 21 CFR 314.50(i)(3), and correctly identifies the relevant statutory section as 21 USC 355(c)(3)(C). However, we would not delay an action under these circumstances (i.e., where the 505(b)(2) applicant is the patent owner) if the substantive issues related to patent certification have been addressed.

Should you have any questions, please do not hesitate to contact me. Thank you.

-- Janice

From: Weiner, Janice
Sent: Tuesday, May 22, 2007 1:09 PM
To: Garcia, Lori
Cc: Colangelo, Kim M; Dickinson, Elizabeth; Dettelbach, Kim; Boocker, Nancy; Bernstein, Michael
Subject: FW: 5/25/07 goal date: [Xyzal] NDA 22-064 patent certification information

Lori,

Thank you for forwarding the patent certification information and correspondence provided by UCB regarding their pending 505(b)(2) application for Xyzal (levocetirizine dihydrochloride) tablets, with a PDUFA goal date of Friday, May 25, 2007. (I've attached, for reference, earlier e-mail correspondence regarding the patent certification issues raised by this application.) If this is the entirety of the planned submission to the NDA, then I would consider it to be inadequate for the reasons discussed below (if others believe that I am taking too stringent an approach, please advise):

UCB provided the following information in the attached submission:
(1) Paragraph IV certification for U.S. Patent No. 4,525,358

(2) Paragraph IV certification for U.S. Patent No. 6,455,533

(3) Letter from Pfizer (Sr. VP, Associate Gen. Counsel, IP) -- undated -- acknowledging receipt of the notice of certification of noninfringement of patents, confirming that Pfizer "owner of U.S. Patents No. 6,455,533 and No. 4,525,358, consents to an immediate effective date of approval of NDA 22-064 and waives the 45-day period of 21 U.S.C. 344(c)(3)(C)."

(4) Letter from UCB S.A., N.V. dated May 9, 2007, confirming that "UCB S.A., owner of U.S. Patent No. 6,455,533, consents to an immediate effective date of approval of NDA No. 22-064 and waives the 45-day period of 21 U.S.C. 344(c)(3)(C)."

(5) Letter from UCB S.A., N.V. -- undated (the 5/14/07 in the footer is inadequate) -- confirming that "UCB S.A., owner of U.S. Patent No. 6,455,533, consents to an immediate effective date of approval of NDA No. 22-157 [levocetirizine dihydrochloride 5 mg/ml oral solution] and waives the 45-day period of 21 U.S.C. 344(c)(3)(C)."
Here are my comments on the submission:

1. UCB's paragraph IV certifications for the '358 and '533 patents are acceptable per the regulations at 21 CFR 314.50(i)(1)(i)(A)(4).

2. The documentation of receipt of notice by Pfizer is inadequate because it is undated. The regulations state that "FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice." (21 CFR 314.52(e)) In light of the waiver of the 45-day period, I am less concerned regarding documentation of

the date of receipt. However, as the Pfizer letter will need to be revised as discussed below, the revised version should be dated.

3. There is no documentation of receipt of notice by UCB S.A. Although it may be inferred by the nature of the correspondence, it is unclear why UCB failed to include a similar acknowledgment of receipt of notice, as in the Pfizer letter. However, as the UCB S.A. letter will need to be revised as discussed below, the revised version should include a documentation of receipt of notice.

4. The letters from both Pfizer and UCB consenting to an immediate effective date are inadequate for the following reasons:
(a) The regulations at 21 CFR 314.50(i)(3) require that "[i]f the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application SHALL CONTAIN A WRITTEN STATEMENT FROM THE PATENT OWNER THAT IT HAS A LICENSING AGREEMENT with the applicant and that it consents to an immediate effective date." (emphasis added) None of the letters reference a licensing agreement (or, if such an agreement is inapplicable because it is a related corporate entity, to provide a statement in this regard).

(b) As noted above, the letter from Pfizer is undated.

(c) All of the letters provide a waiver of the "45-day period of 21 U.S.C. 344(c)(3)(C)." (In case you're wondering, 21 U.S.C. 344 corresponds to section 404 of the Act and deals with Emergency Permit Control for food products. There is no paragraph (3) under subsection (c). I'm tempted to comment further here, but I will refrain from doing so...) The letters should be revised to reference 21 U.S.C. 355 (section 505 of the Act).
5. It had been my understanding that UCB represented to the Division that they were the owners of the '358 and '533 patents, yet they have only provided a letter with respect to the '533 patent. If the sponsor of the Xyzal NDA (UCB, Inc.) is the same corporate entity as the [co-?]owner of the '358 patent, then they should clarify this in writing. (As previously noted, we do require notice of a paragraph IV certification to related corporate entities, but not the same corporate entity.)

6. The second letter from UCB S.A. (undated) references a different NDA for levocetirizine dihydrochloride oral solution, instead of tablets. Revisions consistent with the advice provided above also should be made, although I am not presently aware of the timeframe for an action on that application.

I hope that this is helpful. Should you have any questions, please do not hesitate to contact me. Thank you.

-- Janice

From: Garcia, Lori
Sent: Tuesday, May 22, 2007 9:19 AM

To: Colangelo, Kim M; Weiner, Janice
Subject: FW: [Xyzal] NDA 22-064 patent certification information

Good morning,

Here is the info for NDA 22-064. I have not had a chance to look at it yet--I've got a couple of meetings to go to, but I wanted to get it to you as soon as possible--let me know if they've provided adequate info, or if anything else will be needed.

Thanks,

Lori

From: Tegtmeyer Susan [mailto:Susan.Tegtmeyer@ucb-group.com]
Sent: Monday, May 21, 2007 6:09 PM
To: Garcia, Lori
Subject: NDA 22-064 patent certification information

Hi Lori,

Attached is the patent certification information for NDA 22-064. Please let me know if you have any questions. As mentioned in my previous email, the formal submission to the NDA will follow.

Regards,
Susan

<<...>> <<...>> <<...>> <<...>>

Email #2

From: Tegtmeyer Susan [mailto:Susan.Tegtmeyer@ucb-group.com]
Sent: Wednesday, May 23, 2007 11:57 AM
To: Garcia, Lori
Subject: RE: Patent certification

Lori, I'll follow up on this immediately.
Regards,
Susan

-----Original Message-----
From: Garcia, Lori [mailto:lori.garcia@fda.hhs.gov]
Sent: Wednesday, May 23, 2007 11:55 AM
To: Tegtmeyer Susan
Subject: Patent certification
Importance: High

Dear Susan,

The following issues should be addressed by the UCB with respect to the patent certification information.

In general, it is unclear from your correspondence (email dated 5/21/07, official submission pending) who owns the '358 and '533 patents and the relationship between the UCB entity that submitted the 505(b)(2) application and the UCB entity(ies) that own the listed patents.

1. It was our understanding that UCB (or a related corporate entity) was the owner of the '358 and '533 patents, yet you have only provided a letter (consenting to an immediate effective date of approval of NDA 22-064 and waiving the 45-day period described in 21 USC 355(c)(3)(C)) with respect to the '533 patent. Clarify who owns the '358 patent and, if it is a UCB corporate entity, the relationship between the patent owner and the UCB entity that submitted the 505(b)(2) application for Xyzal. If the sponsor of the Xyzal 505(b)(2) application is the same corporate entity as the owner of the '358 patent, then clarify this in writing. If they are related corporate entities, then we do require notice of a paragraph IV certification and compliance with applicable regulatory requirements.

2. The letter from Pfizer confirms that Pfizer, Inc. owns the '533 and '358 patents. Again, it was our understanding that UCB represented to the Division that UCB (or a related corporate entity) was the owner of the '358 and '533 patents. Clarify, in writing, who owns or co-owns these patents. If Pfizer is not a patent owner, please advise us as to Pfizer's interest in the patent (e.g., is Pfizer a licensee?). Under the circumstances, we would consider a written statement from UCB to be acceptable.

3. It is worth noting that if you make any further submissions or amended submissions, they should ensure that all correspondence is dated, includes documentation of receipt of notice of the

paragraph IV certification (per 21 CFR 314.52(e)), complies with 21 CFR 314.50(i)(3), and correctly identifies the relevant statutory section as 21 USC 355(c)(3)(C). However, we would not delay an action under these circumstances (i.e., where the 505(b)(2) applicant is the patent owner) if the substantive issues related to patent certification have been addressed.

We are requesting a response to these outstanding issues by 1:00pm on Thursday, May 24, 2007, or sooner, if possible.

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

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

/s/

Lori Garcia
5/23/2007 01:49:02 PM
CSO

From: Garcia, Lori
Sent: Thursday, May 24, 2007 2:36 PM
To: 'Tegtmeyer Susan'
Cc: Garcia, Lori
Subject: FW: NDA 22-064/label
Importance: High

Susan,

Two more changes to sections 14.2. And that's it. Any other agreed-upon changes will need to be submitted in the final printed label (in SPL) after action.

> The dose-ranging trial was conducted to evaluate the efficacy of XYZAL 2.5, 5, and 10 mg once daily in the evening. In this trial, each of the three doses of XYZAL demonstrated greater decrease in the reflective pruritus severity score than placebo and the difference was statistically significant for all three doses (see Table 5).
>
> The single-dose level trial evaluated the efficacy of XYZAL 5 mg once daily in the evening compared to placebo in patients with chronic idiopathic urticaria over a 4-week treatment period. XYZAL 5 mg demonstrated a greater decrease from baseline in the reflective pruritus severity score than placebo and the difference from placebo was statistically significant.

From: Garcia, Lori
Sent: Thursday, May 24, 2007 2:05 PM
To: 'Tegtmeyer Susan'
Cc: Garcia, Lori
Subject: RE: NDA 22-064/label
Importance: High

Hi Susan,

To the best of my knowledge, these are the final labeling comments at this point in time, although there may be 1 or two more coming. We will deal with them later if necessary. Please incorporate the revisions into the Xyzal label and email your response to me by the end of today. Additionally, submit your official response to the NDA to me directly via overnight carrier as discussed in a previous email. If you have any questions or concerns regarding our proposed revisions, please call me

1. Table 3 and 5 should have all CI as 95 percent. [redacted] 95 percent. Since these have already been recalculated as noted in your email below, they just need to be incorporated into the label.

2. Section 14 Clinical studies, onset of action for allergic rhinitis:

In the second line insert "in allergic rhinitis patients" after the word "studies" to denote who were the study subjects.

In the third to fourth line, [redacted] 1 hour.". [redacted] The onset of action was at 1 hour, and not at a time point before 1 hour.

3. Be consistent with how you write the "number" while referring to clinical trials. For example, you have written [redacted] Our preference is that you spell out the number when the number of trials is one to nine. Note that this comment only applies to trials and not to anything else.

4. [redacted]

4 weeks and 6 months. [redacted] Make similar changes throughout the label.

5. In the Highlights, Dosage and administration section:

Insert "(1 tablet)" for adults and children 12 years of age and older. This will make it consistent with the next sentence where we have 1/2 tablet in parenthesis.

6. In Highlights, Renal Impairment, the word "kidneys" [redacted] This comment also applies to section 8.6.

7. Section 6.1, line 13. [redacted] to "exposure of 4 or 6 months."

8. Section 13.1 line 3. [redacted] "studies are relevant for determination of the.". Note that we are [redacted] with a more descriptive clause.

9. Section 14. Opening sentence of paragraph 3 does not read very well. We suggest rewriting the opening sentence by breaking the complex sentence into two sentences as follows:

The three dose-ranging trials were conducted to evaluate the efficacy of XYZAL 2.5, 5, and 10 mg once daily in the evening. One trial was 2 weeks in duration conducted in patients with seasonal allergic rhinitis, and two trials were 4 weeks in duration conducted in patients with perennial allergic rhinitis.

Thanks,

Lori

From: Tegtmeyer Susan [mailto:Susan.Tegtmeyer@ucb-group.com]
Sent: Thursday, May 24, 2007 11:25 AM
To: Garcia, Lori
Subject: RE: NDA 22-064/label

Lori,
The recalculation for the 95% CI has been done and we will edit the label accordingly. FYI, I have attached Tables 3 and 5 with the new numbers inserted.

We will also correct sentence 2 in paragraph 2 of the Clinical Trials section to read "five studies" as noted in your email below

Thanks.
Susan
-----Original Message-----
From: Garcia, Lori [mailto:lori.garcia@fda.hhs.gov]
Sent: Wednesday, May 23, 2007 4:43 PM
To: Tegtmeyer Susan

Ui jt !jt !b!sf qsf t f oubjpo!pglbo!f rhduspojd!sf dpse!u bulx bt !t jhof e!f rhduspojdbmm!boe
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6035031181 14; 12; 45! QN
DTP

MEMORANDUM OF EMAIL COMMUNICATION

DATE: May 23, 2007

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: UCB submitted patent certification information via email on 5/21/07 (formal submission to the NDA to follow). The content of this email was reviewed by FDA legal counsel, Janice Weiner, with the Office of Regulatory Policy. It was determined that additional information and clarification was needed from UCB (Email #1). Additional information from UCB was requested via email on 5/23/07 (Email #2).

Lori Garcia, R.Ph.
Regulatory Project Manager

MEMORANDUM OF E-MAIL COMMUNICATION

DATE: May 21, 2007

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: FDA revised labeling and comments in response to draft revised labeling submitted by UCB on May 14, 2007. See e-mail and attachments below.

Lori Garcia, R.Ph.
Regulatory Project Manager

May 21, 2007
XYZAL – labeling comments

1. Revise all cross-references in the FPI to the preferred formatting for PLR labels (e.g., "*[see Warnings and Precautions (5.2)]*"). Note that the cross-reference should name the main section heading, but use the appropriate subsection number in parentheses.

2. The numbering of the subsections in the "Use in Specific Population" section is incorrect. The numbers are dictated by the regulations and do not change even if a section is omitted because it is inapplicable. For example, Nursing Mothers is always 8.3, Pediatric Use is always 8.4, and Geriatric Use is always 8.5. Any subsections added after that can be created as needed. Revise the subsection numbers to be consistent with the regulations. Ensure that changes are also made in Contents and in all cross-references throughout the FPI and Highlights.

3. Revise the order of the dosage strength in the Clinical Trials section Tables 3 and 5 so that the highest strength appears last (i.e. 2.5mg, 5 mg, 10 mg).

4. In the Clinical Trials section (14) the subsection heading [redacted] You may propose an alternate subheading to replace them. Alternatively you may choose to [redacted] subheadings from the clinical trials Description and leave only the two bolded headings "Seasonal and Perennial Allergic Rhinitis" and Chronic Idiopathic Urticaria."

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On Original

MEMORANDUM OF TELECON

DATE: May 8, 2007

APPLICATION NUMBER: NDA 22-064

BETWEEN:

Name:

Regulatory Affairs
Patty Fritz
Susan Tegtmeyer
Anisa Dhalla
Mary-Beth Wigley (sanofi-aventis)
Clinical Development
Catherine Arendt
Pharmacokinetics
Margherita Strolin-Benedetti
Statistics
Anne Danniau
Jean Lecot
Dominique Rosillion
Nonclinical
Michael Canning
Rhys Whomsley
Medical Affairs
Jean-Marc Haeusler
George Georges (sanofi-aventis)
Drug Safety
Vicky Geskin

Phone: 770-970-8654
Representing: UCB Pharma

AND

Name:

Division of Pulmonary and Allergy Products
Lori Garcia, R.Ph., Regulatory Project Manager
Lydia Gilbert-McClain, M.D., Clinical Team Leader
Badrul A. Chowdhury, Division Director
Robert Boucher, Clinical Reviewer
Emmanuel O. Fadiran, Clin Pharm Team Leader
Partha Roy, Clin Pharm Reviewer
Lawrence F. Sancilio, Pharm/Tox Reviewer
Ching-Long J. Sun, Pharm/Tox Team Leader
Qian H. Li, Statisics Team Leader

SUBJECT: Labeling negotiations

A teleconference was held to discuss UCB's draft labeling submitted on May 2, 2007, in response to the revisions proposed by the Division in a facsimile dated April 17, 2007.

Revisions were mutually agreed-upon and UCB agreed to submit the revised draft labeling by May 11, 2007.

The Division noted that the label was still under review by other groups within the FDA and that additional recommendations regarding the labeling may be forthcoming.

_____

Lori Garcia, R.Ph.
Regulatory Project Manager

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/s/

Lori Garcia
5/10/2007 10:21:31 PM
CSO

INTEROFFICE MEMO

TO: NDA 22064
FROM: C. Joseph Sun, Ph. D., Supervisory Pharmacologist
Division of Pulmonary and Allergy Products
DATE: May 8, 2007

I concur with the pharmacologist's recommendation that pharmacology and toxicology of levocetirizine tablets have been adequately studied and that the drug product is approvable from a preclinical standpoint.

Levocetirizine is the R-enatiomer of cetirizine. Preclinical Pharmacology and toxicology assessment of levocetirizine is primarily based on a prior FDA finding of safety and effectiveness for cetirizine tablets (NDA 19835) with the supplemental pharmacology and genotoxicity assessment of levocetirizine , 4- and 13- week bridging toxicity studies in rats and dogs and embryo-fetal bridging studies in rats and rabbits comparing the toxicity profile of levocetirizine with cetirizine.

Pharmacology: Levocetirine is a competitive H_1 receptor antagonist. It has been demonstrated more potent than cetirizine in blocking H_1 receptors in different tissues, blocking the response to histamine in isolated tissue preparations and in vivo animal models.

General toxicity: Chronic toxicity of cetirizine has been extensively investigated in mice, rats and dogs. The liver (enzyme induction and fat deposition) was the target organ of toxicity in mice and rats. In dogs, the target organ of toxicity was the gastrointestinal system with the major sign being emesis. In the bridging 4-week and 13-week comparative toxicity toxicities of levocetirine and cetirizine, similar target organs of toxicity were identified in rats and dogs and there were no apparent differences in the toxic effects between levocetirizine and cetirizine.

Reproductive toxicity: No fertility and prenatal and postnatal studies were preformed with leveocetirine. Therefore, evaluation of cetirizine determined that there was no impairment of fertility in mice and rats, no teratogenic findings in rats and rabbits and no effects on prenatal and postnatal development other than increased skeletal anomalies/variants in rabbits and lower pup weight in mice. Embyrofetal development studies of levecetirizine revealed no teratogenic effects in rats and rabbits. Thus, pregnancy category B is appropriate.

Genotoxicity: Levocetirizine was negative in the Ames test, chromosome aberration assay in human lymphocytes, mouse lymphoma assay and mouse micronucleus assay.

Carcinogencity: No carcinogenicity studies were performed with levocetirizine. Its carcinogenicity assessment was based on studies conducted with cetirizine in mice and

rats. Cetirizine was not carcinogenic in rats, but caused an increased incidence of benign liver tumor in male mice.

Labeling: Carcinogenesis, mutagenesis and impairment of fertility and pregnancy category B sections have been incorporated with the above-mentioned preclinical findings.

There are no outstanding preclinical issues.

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/s/

Joseph Sun
5/8/2007 05:36:44 PM
PHARMACOLOGIST

MEMORANDUM OF EMAIL COMMUNICATION

DATE: May 1, 2007

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: Patent issues with UCB's 505(b)(2) NDA 22-064. After discussion with Janice Weiner (Office of Regulatory Policy), the sponsor was notified via email of the following recommendations from the Agency.

From: Garcia, Lori
Sent: Tuesday, May 01, 2007 9:06 PM
To: 'Tegtmeyer Susan'
Subject: patent issues

Hi Susan,

The "no relevant patents" statement provided in your application is not accurate -- there are patents listed in the Orange Book for the listed drugs (Zyrtec tablets (19-835), Zyrtec syrup (20-346), and Zyrtec chewable tablets (21-621)) relied upon by you in support of your 505(b)(2) application. The '358 patent is listed for all three NDAs, and the '533 patent is listed only for Zyrtec chewable tablets. You should submit either a paragraph III or paragraph IV certification -- based upon your representation that UCB owns the patent(s) at issue, it would appear that a paragraph IV certification is appropriate.

Assuming that UCB's representation regarding patent ownership is accurate (and please note that FDA does not assess the accuracy of which party owns which patent), there is no statutory exception to patent certification and notice requirements for a 505(b)(2) applicant/patent owner relying upon the Agency's finding of safety and/or effectiveness for a listed drug owned by another entity.

Section 505(b)(3)(C) of the Act requires that a 505(b)(2) applicant that makes a paragraph IV certification provide notice to the NDA holder for the drug claimed by the patent and each owner of the patent at issue (see also 21 CFR 314.52(a)). Accordingly, UCB would be required to provide notice to:

(1) Pfizer, the NDA holder for Zyrtec, and

(2) The owner(s) of the '358 and '533 patent. If, as UCB suggests, the same corporate entity that submitted the 505(b)(2) application owns the patent, then UCB should provide the Agency with a statement confirming this. If the 505(b)(2) applicant is not the same as the entity that owns the patent, then notice to the related corporate entity will be required (and the related corporate entity may provide a

written statement consenting to an immediate effective date, per our regulations at 21 CFR 314.50(i)(3), prior to expiration of the 45-day period).

UCB also may elect to request from Pfizer a written statement consenting to an immediate effective date upon approval of the 505(b)(2) application and waiving the 45-day period.

Please contact me if you have any additional questions.

Best Regards,

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
5/1/2007 09:30:59 PM
CSO

MEMORANDUM OF TELECON

DATE: April 19, 2007

APPLICATION NUMBER: NDA 22-064

BETWEEN:

Name: Susan Tegtmeyer
Phone: PHONE #
Representing: UCB, Inc.

AND

Name: Lori Garcia
Division of Pulmonary and Allergy Products

SUBJECT: Patent certification

UCB was notified that they did not certify to the two patents listed in the Orange Book for Zyrtec (cetirizine), the reference listed drug for their 505(b)(2) NDA 22-064, as required by section 505(b)(2) of the act. The sponsor was also referred to 21 CFR part 314. The sponsor stated that they would take care of this issue immediately and would notify their legal department.

Lori Garcia, R.Ph.
Regulatory Project Manager

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4/23/07
5/1/07

NDA 22-064

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

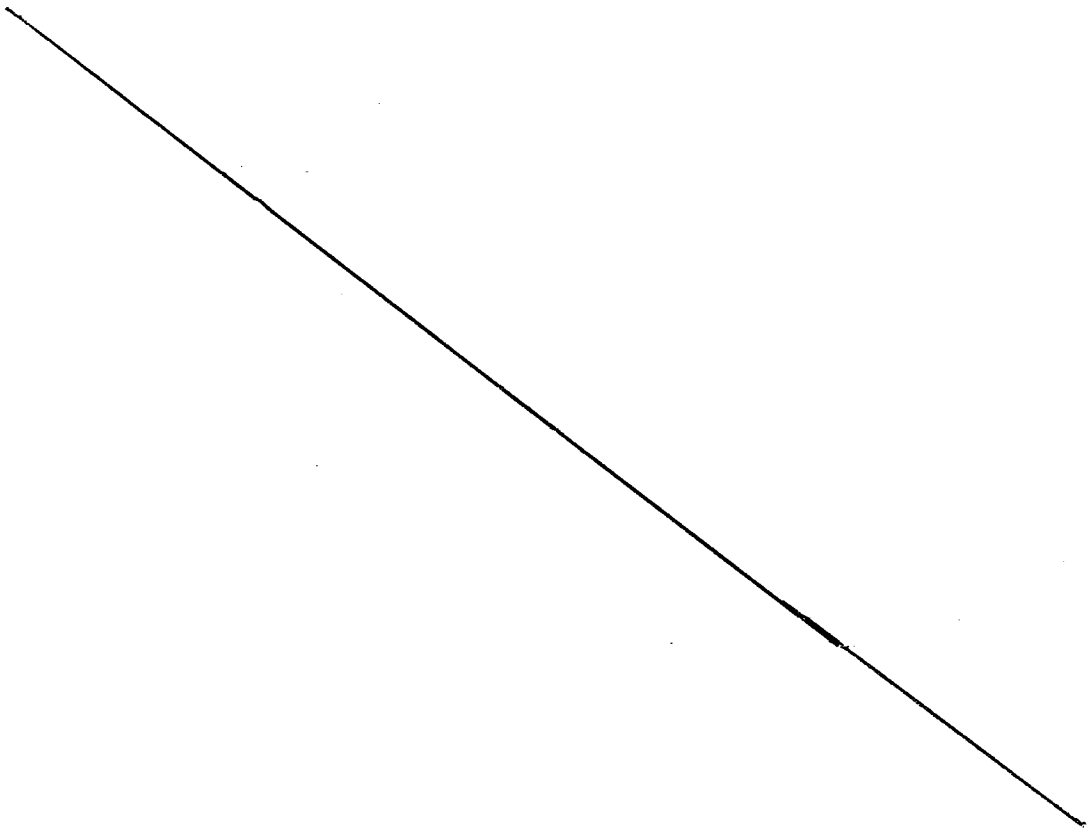
Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

Dear Ms. Fritz:

Please refer to your new drug application dated July 24, 2006, received July 25, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyzal (levocetirizine dihydrochloride) 5mg Tablets.

We also refer to your submission dated January 22, 2007.

The following comments and recommendations are regarding the carton, blister and container labeling for the Xyzal:



1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

We request that you submit your revised draft carton/container/blister labeling and/or comments by May 14, 2007. Note that any questions regarding these labeling comments may also be addressed at the teleconference scheduled for Tuesday, May 8, 2007, from 3:15pm-4:00pm EST.

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

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DTP

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-064

Name of Drug: Xyzal (levocetirizine dihydrochloride) 5mg Tablets

Applicant: UCB, Inc.

Material Reviewed:

Submission Date(s): September 19, 2006

Receipt Date(s): September 20, 2006

Submission Date of Structured Product Labeling (SPL): September 19, 2006

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

General Comments

1. We remind you that the font size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

3. Refer to the Institute of Safe Medication Practices' website

(http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

4. Avoid international spelling (e.g., use "hematologic," not [redacted]

Highlights

5. We remind you that the Highlights section must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

6. The Initial U.S. Approval date should [redacted]

7. Regarding Contraindications, "theoretical" possibilities must not be listed (e.g., hypersensitivity). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]

8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

9. The Patient Counseling Information statement must appear in Highlights and must read: See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

10. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval.

Contents

11. Include only section and subsection headings in Contents. Headings within a subsection (i.e., sub-subsection headings) must not be included in the Contents.

12. The footnote "*Sections of subsections omitted from the full prescribing information are not listed" should be right-justified. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

13. Delete "Category B" from the subsection 8.1 Pregnancy. The same applies for the FPI. [See 21 CFR 201.56(d)(1)].

14. Regarding section **13 NONCLINICAL TOXICOLOGY**, [redacted] the subsection heading 13.1 so that it reads Carcinogenesis, Mutagenesis, Impairment of Fertility. The same applies for the FPI.

15. Include the section heading for **17 PATIENT COUNSELING INFORMATION**. [See 21 CFR 201.57(b)]

Full Prescribing Information (FPI)

16. In section **3 DOSAGE FORMS AND STRENGTHS**, include the identifying characteristics of the dosage forms, such as shape, color, coating, scoring, and ***imprinting*** when applicable. [See 21 CFR 201.57(c)(4)(ii)]

17. The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. For example, *[see Clinical Pharmacology (12)]*, not (See CLINICAL PHARMACOLOGY). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use bold print. Do not use all capital letters. Please fix all cross-references throughout the labeling. [See Implementation Guidance]

18. Indent all paragraphs, headings, subheadings throughout the FPI. For overall FPI formatting, refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

19. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.3.1 Absorption, Distribution, Metabolism, Elimination and Drug Interaction Studies). Sub-subsection headings should not be numbered (e.g., Absorption, Distribution, Metabolism, Elimination and Drug Interaction Studies).

20. Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance.

21. In section **16 HOW SUPPLIED/STORAGE AND HANDLING,** include information as required under 21 CFR 201.57(c)(17), e.g., dosage strength and dosage form shape, color, coating, scoring and imprinting, when applicable.

22. **17 PATIENT COUNSELING INFORMATION** must follow after **16 HOW SUPPLIED/STORAGE AND HANDLING** section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient, but rather for the prescriber, so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

Recommendations

UCB, Inc. should address the identified deficiencies/issues and re-submit labeling by April 30, 2007. These comments will be sent with the FDA's first draft revision of the labeling following the wrap-up meeting.

Lori Garcia, R.Ph.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: LGarcia/March 12, 2007
Revised/Initialed:
Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

Ui jt !jt !b!sf qsf t f oubjpo!pgbo!f rhduspojd!sf dpse!ui bux bt !t jhof e!f rhduspojdbm!boe
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4/20/07

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-064 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Xyzal
Established Name: levocetirizine dihydrochloride
Strengths: 5mg tablets

Applicant: UCB, Inc
Agent for Applicant (if applicable):

Date of Application: July 24, 2006
Date of Receipt: July 25, 2006
Date clock started after UN:
Date of Filing Meeting: September 12, 2006
Filing Date: September 23, 2006 (RTF action issued on 9/22/06, was overturned on 10/17/06, and the application was filed effective 9/23/06).
Action Goal Date (optional): User Fee Goal Date: May 25, 2007

Indication(s) requested: SAR, PAR, CIU in adults and children 6 yrs of age and older

Type of Original NDA: (b)(1) ☐ (b)(2) X☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES X☒ NO ☐

User Fee Status: Paid X☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☒

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, X 5 Years No ☐
  NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES ☒ N ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: PIND 72,233
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) N/A NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) N/A NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) N/A NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? ☒ 9/17/06 ☐ NO
  YES
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐

	If EA submitted, consulted to EA officer, OPS?	YES ☐	NO ☐
•	Establishment Evaluation Request (EER) submitted to DMPQ?	YES ☒	NO ☐
•	If a parenteral product, consulted to Microbiology Team? N/A	YES ☐	NO ☐

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ATTACHMENT

MEMO OF FILING MEETING

DATE: September 12, 2006 (filing meeting)
October 23, 2006 (planning meeting)

NDA #: 22-064

DRUG NAMES: Xyzal (levocetirizine dihydrochloride) 5mg Tablets

APPLICANT: UCB, Inc.

BACKGROUND:
NDA for submitted July 24, 2006, for approval to market Xyzal (levocetirizine dihydrochloride) 5mg Tablets 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. No US IND submitted. Previous correspondence has been submitted under PIND 72,233. This is a 505(b)(2) NDA and references the approved drug procuct Zyrtec (cetirizine hydrochloride).

ATTENDEES:
September 12, 2006, filing meeting: Badrul Chowdhury, Lydia Gilbert-McClain, Robert Boucher, Ruthie Davi, James Gebert, Steve Kuprel, Larry Sancilio, Tim McGovern, Partha Roy, Tayo Fadiran, Art Shaw, Prasad Peri, Leah Ripper, Curt Rosebraugh, Robert Meyer.

October 23, 2006, planning meeting:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Robert Boucher
Secondary Medical:	
Statistical:	James Gebert
Pharmacology:	Larry Sancilio
Statistical Pharmacology:	
Chemistry:	Art Shaw
Environmental Assessment (if needed):	
Biopharmaceutical:	Partha Roy
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Lori Garcia
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐

If no, explain:

- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX	N/A ☐	FILE ☒	REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY	FILE ☒	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒

  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ **Filing issues to be communicated by Day 74. List:

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

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 [redacted]

[redacted]

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.

**Note: Issues identified were communicated on Day 59 (9/22/06) in a refuse-to-file letter. Issue #1 was a refuse to file issue. Issues A, B and C were filing review issues. The RTF action was rescinded and a "fileable" letter was issued October 17, 2006.

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Lori Garcia, R.Ph., Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Zyrtec (cetirizine HCl): NDA 19-835; NDA 21-621; NDA 20-346

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c).

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☒ NO ☐

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **Levocetirizine is the R-enantiomer of the approved racemate Zyrtec (cetirizine).**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☒

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 4525358, 6455533

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☒

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☒ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☒ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration
19-835, 20-346, 21-621	**4525358**	**PED**	**12/25/07**

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/s/

Lori Garcia
4/20/2007 01:53:49 PM
CSO

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
4/20/2007 05:31:57 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-064

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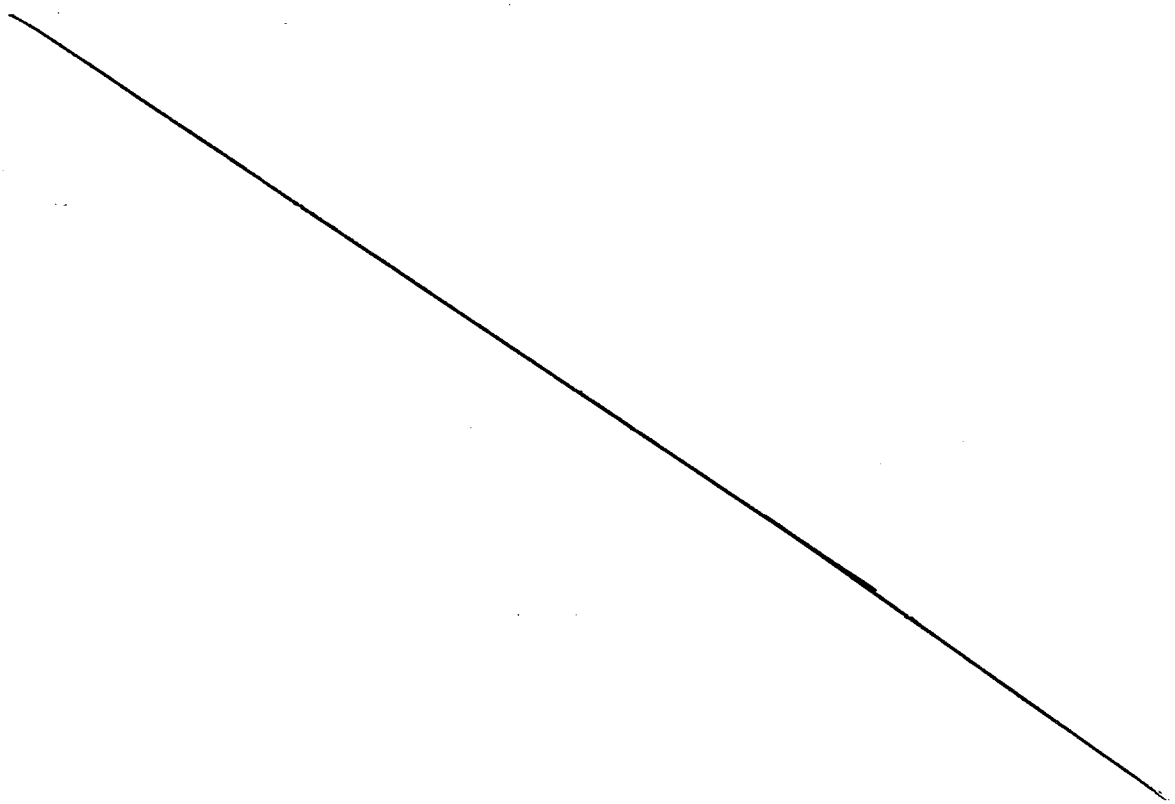

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Sincerely,

{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
4/20/2007 05:31:57 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 4/17/07

TO: Lori Garcia, Regulatory Project Manager
Bob Boucher, M.D., Clinical Reviewer
Division of Pulmonary and Allergy Products, HFD-570

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Tejashri Purohit-Sheth, M.D.
Clinical Reviewer, GCP 2, HFD-47
Division of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections, Pending Receipt of EIRs

NDA: 22-064

NME: No

APPLICANT: UCB Pharma

DRUG: Xyzal® (levocetirizine dihydrochloride)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Allergic Rhinitis, Urticaria

CONSULTATION REQUEST DATE: 10/26/06

DIVISION ACTION GOAL DATE: 4/25/07

PDUFA DATE: 5/25/07

I. BACKGROUND:

UCB Pharma, Inc. submitted this New Drug Application for the use of levocetirizine dihydrochloride (Xyzal®) 5 mg oral tablets for the treatment of symptoms of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria, the same indications as cetirizine.

The pivotal study for the indication in Perennial Allergic Rhinitis (A00266) and the pivotal study for the indication in Seasonal Allergic Rhinitis (A00268) were selected for DSI audit. Both studies were conducted at numerous sites in South Africa. For Study A00266 Dr. Paul Potter's and Dr. Christiaan De Villiers' sites were selected for inspection; for Study A00268, Dr. Paul Potter's site was selected. These sites were selected for audit due to high enrollment.

II. RESULTS (by protocol/site):

Name of CI and site #	City, State*	Country	Protocol #	Insp. Date	EIR Received Date	Final Classification
Dr. Paul Potter, Site 001	Western Cape	South Africa	A00266 A00268	Unknown	Pending	Pending
Dr. Christian DeVilliers, Site 005	KwaZulu	South Africa	A00266	2/26-2/28/06	Pending	Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

1. **Dr Paul Potter: Site# 001**
   UTC Lung Institute
   Corner George & Falmouth Street
   Observatory 7925
   Western Cape, South Africa
   Patients enrolled: 23

   a. What was inspected?
   A total of 23 and 20 subjects were randomized to this site for Studies A00266 and A00268, respectively. Data audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. Informed Consent was verified in 100% of subjects. The audit included comparison of source documentation to CRFs and data listings provide in the NDA.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary
Generally, the investigator was found to have executed the study adequately, although a couple minor deviations from FDA regulations were noted. No FDA Form 483, Inspectional Observations, was issued to the investigator. Per email communication with the field inspector, no significant discrepancies affecting data integrity were detected.

d. Assessment of data integrity:
The data from Dr. Potter's site appear acceptable as collected and generated for both pivotal studies; however, note that this conclusion is based on preliminary communication with the field inspector. Upon receipt of the EIR, if there are any substantial changes to this assessment, the review division will be notified.

2. **Dr. Christian T. DeVilliers: Site# 005**
20 David Street
Scottsburgh South 4180
KwaZulu Natal, South Africa
Patients enrolled: 24

a. What was inspected?
A total of 24 subjects were randomized to this site and data audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The audit included comparison of source documentation to CRFs and data listings provided in the NDA.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the FAXed 483.

c. General observations/commentary
Generally, the investigator was found to have executed the study adequately, although a couple deviations from FDA regulations were noted, and an FDA Form 483 was issued for these observations (described below). Study elements appeared well organized and complete and in the English language. Subject records were consistent with diagnosis and description provided in the NDA.

Notable findings from the FDA Form 483 that was issued are summarized below:

- Study subject #098 signed informed consent form to participate in protocol #A00266 on 20 Jun 2000. However, laboratory testing was performed on 19

Jun 2000. According to Dr. DeVilliers, based on laboratory results received on 19 Jun 2000; this patient was recruited for enrollment in this study.

- Case report forms were inaccurate, in that, no adverse events were reported to sponsor of protocol #A00266 for study subject #105. Source records for study subject #105 enrolled in protocol #A00266 reported an adverse event on 3 Jul 2000 and another adverse event on 24 Jul 2000.

- Protocol #A00266 required that if an ECG is performed at Visit 1, another ECG must be recorded at Visit 3 one hour after investigational drug intake in the presence of the clinical investigator. However, at Visit 3, the ECG was performed two hours after drug intake.

Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the official EIR.

d. Assessment of data integrity:
The data from Dr. DeVillier's site appear acceptable as collected and generated according to the original protocol. Although some regulatory violations were noted, it is unlikely that these would affect the final outcome of the study with respect to efficacy or safety.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Per preliminary communications with the field inspector, the studies were executed appropriately at both Dr. Potter's and Dr. DeVilliers' sites. The few regulatory violations documented are unlikely to affect the outcome of the study. The study data collected by Drs. Potter and DeVilliers appears acceptable in support of the proposed indications.

Follow-Up Actions:
Observations noted above are based on the Form FDA 483 and communications with the field investigator. DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Medical Officer
Good Clinical Branch II
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Tejashri Purohit-Sheth
4/18/2007 03:22:35 PM
MEDICAL OFFICER

Leslie Ball
5/1/2007 12:38:25 PM
MEDICAL OFFICER

Garcia, Lori

From: Shaw, Arthur B
nt: Thursday, April 05, 2007 10:23 AM
: Fraser, Blair; Peri, Prasad
Cc: Shaw, Arthur B; Garcia, Lori
Subject: NDA 22064 Xyzal

I just received the amendment in response to our DR letter. All the issues have been addressed. There were no show-stoppers to begin with.

The only issue is testing for microbial quality. This product has been manufactured and sold world-wide for years. They provided data from 20 batches showing it passed every one. In addition they provided data from 3 stability batches that showed it passed at 0 and 60 months.

No need for a micro consult. I am ready to accept their proposal.

Art Shaw

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

2 April 2007

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

Dear Lori Garcia,

Enclosed are the samples of the imprinted Xyzal® 5mg tablet (NDA 22-064) that you requested.

If you have any questions, please do not hesitate to contact me at 770-970-8595 or at sherri.thrower@ucb-group.com.

Best regards,

Sherri N Thrower

Sherri N Thrower
CMC Regulatory Affairs Associate

MEMORANDUM OF TELECON

DATE: March 28, 2007

APPLICATION NUMBER: NDA 22-064

BETWEEN:

Name: Susan Tegtmeyer
Phone: 770-970-8654
Representing: UCB Pharma

AND

Name: Lori Garcia, R.Ph., Regulatory Project Manager
Lydia Gilbert-McClain, M.D., Clinical Team Leader
Division of Pulmonary and Allergy Products

SUBJECT: Labeling review update

UCB was notified that the Division is at the end of the eighth month of the review cycle for XYZAL and that consistent with the GRMP guidance, we had our wrap up meeting this week.

The Division notified UCB of its plan to forward a copy of the FDA-revised label in approximately 1 week. The Division noted that the review of the application is still ongoing and that the revisions made to the label are not final or all-inclusive. It is likely that additional changes may be forthcoming. UCB was notified that the major labeling revisions thus far:

- reflect the findings of our review (up until this point in time).
- include several changes which were made to bring the label into compliance with the new PLR requirements.
- include the addition of a new section: Section 17 Patient Counseling Information (PLR requirement).
- include major changes to the Clinical Trials section of the label as well as the Adverse reactions section of the label. Extensive revisions have been made to these sections.

The Division requested that UCB respond to the draft FDA-revised version of the label within 1 week from the date that it is received by UCB. A labeling teon could be held after UCB's response is received by the Division to address any issues/comments.

The Division noted that the labeling review is being done to be consistent with the GRMP guidance. The provision of draft FDA-revised labeling is not a signal of any particular regulatory action that is planned for the application.

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/s/

Lori Garcia
3/28/2007 04:11:14 PM
CSO

Garcia, Lori

From: Gilbert McClain, Lydia I
Sent: Wednesday, March 21, 2007 9:40 AM
To: Garcia, Lori; Sancilio, Lawrence F; Sun, Ching-Long J; Peri, Prasad; Shaw, Arthur B; Boucher, Robert; Chowdhury, Badrul A
Subject: NDa - 22-064 -Levoceterizine

Colleagues:
I' ve just returned from the Clinical Pharmacology briefing for this NDA and contrary to our discussion at our first labeling meeting a couple weeks ago, the Clinical Pharmacology recommendation for children 6 -11 is that the drug should be approved at a dose of 2.5 mg. This is based on their determination that the cited literature reference provides good enough PK data from which they can draw conclusions on dosing in this age group. From the cited reference, the 5 mg dose results in ~ twice the exposure as the adults. Given the dose-proportionality of the PK from other studies, they feel comfortable in making a dosing recommendation of 2.5mg for children 6 - 11 years of age. They plan to describe the PK results from the literature in the PK section/Pediatric section of the label. Just thought I'd let you know since we're all working on the label and their recommendation on approving the 6-11 year olds will affect certain sections of the label that you might be working on.
Thanks
Lydia
P.S. If Clin[Pharm is satistified with the information captured in the literature, I think there recommendation is reasonable. We have safety information in 243 children 6 -11 years of age with the 5mg dose.

Lydia I Gilbert-McClain, MD, FCCP
Medical Team Leader
Division of Pulmonary and Allergy Products
US Food and Drug Administration
White Oak Building 22/Room 3310
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2300
Fax. (301) 796 -9718
email. lydia.gilbertmcclain@fda.hhs.gov

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

REQUEST FOR CONSULTATION

TO *(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
March 13, 2007		NDA 22-064	Original NDA	January 22, 2007

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 carton/container/blister labels submittted on 1/22/07 to NDA 22-064 for Xyzal (levocetirizine) 5mg Tablets . These labels are available in the EDR.
If you have any questions, please contact me at 301-796-1212.
Wrap-up meeting: March 26, 2007; 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

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

/s/

Lori Garcia
3/13/2007 03:15:12 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

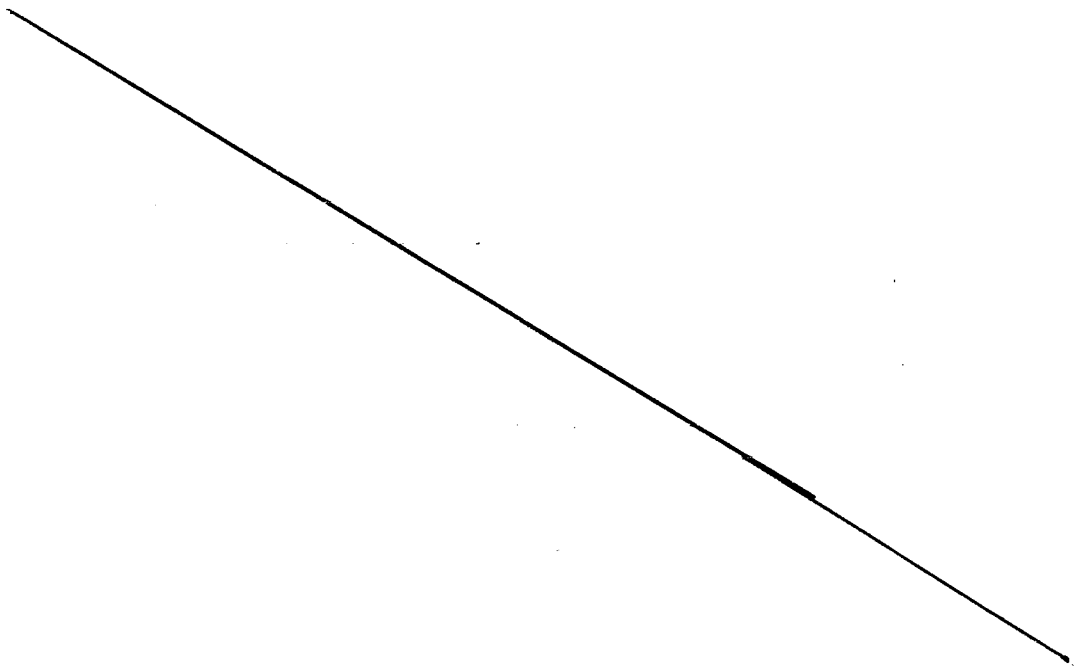
Attention: Patricia Fritz
Vice President
Global Regulatory Affairs

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:



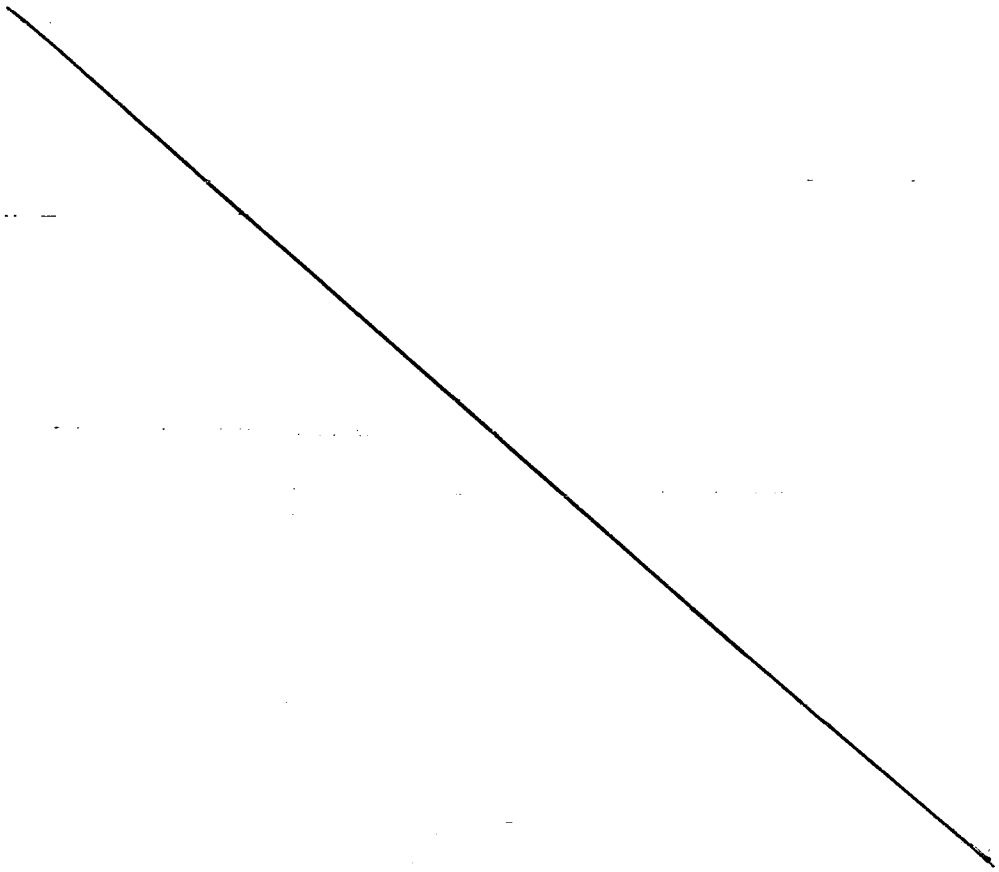
6 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

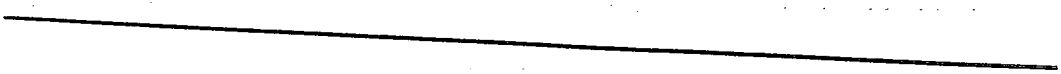
_____ Deliberative Process

Withheld Track Number: Administrative- 2



14. Regarding the labeling:

a. Amend the following sentence in the "Description section from:



to:

"Levocetirizine dihydrochloride is the R enantiomer of cetirizine hydrochloride, a racemic compound with antihistaminic properties"

b. Change the yellow color for the words "5 mg tablet" to make them darker in order to increase the contrast.