CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-285

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

PATENT CERTIFICATION

In the opinion of, and to the best knowledge of, UCB, Inc., there are no patents (other than the patents owned by UCB Societe Anonyme, Belgium, itself) that claim the drug or drugs on which investigations relied upon in this application were conducted or that claim a use investigated or for which approval is sought.

Patricia A. Fritz, MS, RAC
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: 04/30/10
See OMB Statement on Page 3.

NDA NUMBER
22-285

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)
Keppra XR extended release tablet

ACTIVE INGREDIENT(S)	STRENGTH(S)
levetiracetam	500 mg

DOSAGE FORM
Tablet; Oral

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
4,943,639	7/24/1990	7/14/2008

d. Name of Patent Owner	Address *(of Patent Owner)*	
UCB Societe Anonyme	Alle de la Recherche, 60	
	City/State 1070 Bruxelles	
	ZIP Code Belgium	FAX Number *(if available)* (322) 559-9409
	Telephone Number (322) 559-9456	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.)*	
☞ UCB, Inc.	1950 Lake Park Drive	
	City/State Smyrna, GA	
	ZIP Code 30080	FAX Number *(if available)* (770) 970-8345
	Telephone Number (770) 970-7500	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 Graphics (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.**		
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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) *(as listed in the patent)*	Does (Do) the patent claim(s) 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.)*	

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 A P A.	10/26/07

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 Paris	
Address 1950 Lake Park Drive	City/State Smyrna, GA
ZIP Code 30080	Telephone Number (770) 970-8451
FAX Number *(if available)* (770) 970-8483	E-Mail Address *(if available)* richard.paris@ucb-group.com

Attachment for Form FDA 3542a

Part 2.2

Applicant also wishes to note that, in completing Form FDA 3542a for US Patent No. 4,943,639, Applicant has interpreted Question 2.2 to ask whether the patent claims are limited to a different polymorph of the active ingredient described in the approved NDA. The claims of the patent are not limited to any particular polymorph and hence claim the form of the active ingredient described in the approved NDA (as well as other forms, should they exist), and the patent is submitted for listing on that basis. Because the patent claims the form of the active ingredient described in the approved NDA, testing of other forms is not relevant, and Applicant has accordingly answered Question 2.2 in the negative.

24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 7

EXCLUSIVITY SUMMARY

NDA # 22-285 SUPPL # HFD # 120

Trade Name Keppra XR Extended-Release Tablets

Generic Name levetiracetam

Applicant Name UCB, Inc.

Approval Date, If Known 9-12-2008

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)(1)

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?

3 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?

No.

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# 21-035 Keppra Tablets

NDA# 21-505 Keppra Oral Solution

NDA# 21-872 Keppra Injection

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:

Pivotal efficacy and safety study with LEV XR 2 x 500 mg once daily as add-on therapy in refractory epilepsy patients ages 12-70 years with partial onset seizures

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"):

Pivotal efficacy and safety study with LEV XR 2 x 500 mg once daily as add-on therapy in refractory epilepsy patients ages 12-70 years with partial onset seizures

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: Investigations not conducted under an IND.	! Explain:
Investigation #2	!
YES ☐	! NO ☐
Explain:	! 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: Susan Daugherty
Title: RPM
Date: 9/24/08

Name of Office/Division Director signing form: Russell Katz, M.D.
Title: Division Director

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/

Russell Katz
10/3/2008 04:28:38 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-285 | Supplement Number: N/A | NDA Supplement Type (e.g. SE5): N/A

Division Name: DNP | PDUFA Goal Date: September 14, 2008 | Stamp Date: 11/14/2007

Proprietary Name: Keppra XR

Established/Generic Name: levetiracetam

Dosage Form: Extended-Release Tablets, 500 mg

Applicant/Sponsor: UCB, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) N/A
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

* ***Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: KEPPRA XR is an antiepileptic drug indicated for adjunct therapy in the treatment of Partial Onset Seizures in patients [redacted] years of age with epilepsy.) b(4)

Q3: Does this indication have orphan designation?

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

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	__ yr. 0 mo.	12 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☒ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☒ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☒ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): We are waiving the pediatric study requirement for ages 0 to 12 years because the formulation is not appropriate for this age group and Keppra oral Solution is available..

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☒	Other	12 yr. __ mo.	16 yr. __ mo.	☒	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): 09/2012							

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☒ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in

conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies,

proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification)**

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 4/2008)

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

/s/

Susan B. Daugherty
9/24/2008 12:30:04 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.

Elizabeth Kazazian
Director, Global Clinical Quality Assurance

(770) 970-7500

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-285 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Keppra XR™ Extended-Release Tablets
Established Name: levetiracetam
Strengths: 500 mg

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

Date of Application: November 13, 2007
Date of Receipt: November 14, 2007
Date clock started after UN:
Date of Filing Meeting: January 10, 2008
Filing Date: January 12, 2008
Action Goal Date (optional): User Fee Goal Date: September 14, 2008

Indication(s) requested: adjunctive therapy to treat partial onset seizures in adults and adolescents [redacted] years of age and older with epilepsy. b(4)

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
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 ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

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

User Fee Status: Paid ☒ 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:

  NDA 21-872 Keppra Injection – New Drug Formulation exclusivity until 7-31-09

  NDAs 21-035 Keppra Tablets and 21-505 Keppra Solution –
  1. New Patient population exclusivity until June 21, 2008
  2. indication exclusivity - adjunctive treatment for myoclonic seizures in adults with juvenile myoclonic epilepsy until August 15, 2009

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)]? 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? 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?

Forms and certifications requiring an original signature.

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, 3 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 ☒ NO ☐
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: 45,151; 76,812; and Pre-IND 73,703

- 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) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 1, 2007 NO ☐
  If yes, distribute minutes before filing meeting.

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

- Pre-IND Meeting April 19, 2006

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  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:

- 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?
  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? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 10, 2008

NDA #: 22-285

DRUG NAMES: Keppra XR (levetiracetam) Extended-Release Tablets

APPLICANT: UCB, Inc.

BACKGROUND: UCB, Inc. has active NDAs for Keppra Tablets (NDA [redacted], Keppra Oral Solution (NDA 21-505) and Keppra IV (NDA 21-872), which are currently approved for adjunctive therapy to treat partial onset seizures in adults and adolescents 12 years of age and older with epilepsy. b(4)

ATTENDEES: Katz, Russell G; Hershkowitz, Norman; Freed, Lois M; Fisher, J Edward; Heimann, Martha R; Sheridan, Philip; Wu, Ta-Chen; Jin, Kun; Luan, Jingyu; Parepally, Jagan

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

Discipline/Organization	Reviewer
Medical:	Philip Sheridan, M.D.
Statistical:	Jingyu Luan, Ph.D.
Pharmacology:	Edward Fisher, Ph.D.
Chemistry:	David Claffey, Ph.D.
Environmental Assessment (if needed):	
Clinical Pharmacology:	Ta-Chen Wu, Ph.D.
DSI:	
OPS:	
Regulatory Project Management:	Susan Daugherty
Other Consults:	DMETS, DDMAC

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 (optional):

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.

Susan Daugherty
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):

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").

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 YES ☐ NO ☐

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).

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):

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

---

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/s/

Susan B. Daugherty
9/24/2008 12:11:30 PM
CSO

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Wednesday, September 10, 2008 4:53 PM
To: 'Noa Linda'
Subject: NDA 22-285 Keppra XR - comment

Dear Linda,

I am forwarding a comment from the Clinical Pharmacology Reviewer for NDA 22-285:

> *Please evaluate all of the available data (PK and safety) for levetiracetam to understand any differential PK or safety of levetiracetam in Hispanic patients because they had significantly higher (40%) trough concentrations in study N01235 than did Caucasian patients with Keppra XR.*

b(4)

Please let me know if you have any questions.

Best Regards,
Susan

Susan Daugherty
Project Manager
FDA/CDER/OND
Division of Neurology Products
10903 New Hampshire Avenue, Bldg. 22, Rm. 4350
Silver Spring, MD 20993-0002
(301)796-0878

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/s/

Susan B. Daugherty
9/10/2008 04:57:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-285

INFORMATION REQUEST LETTER

UCB, Inc.
Attention: Cassie Buckhalt, Regulatory Affairs Associate
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Buckhalt:

Please refer to your new drug application (NDA) dated November 13, 2007, received November 14, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Keppra XR™ (levetiracetam) Extended-Release Tablets, 500 mg.

We also refer to your submissions dated November 29, 2007, February 15, 2008 and March 21, 2008.

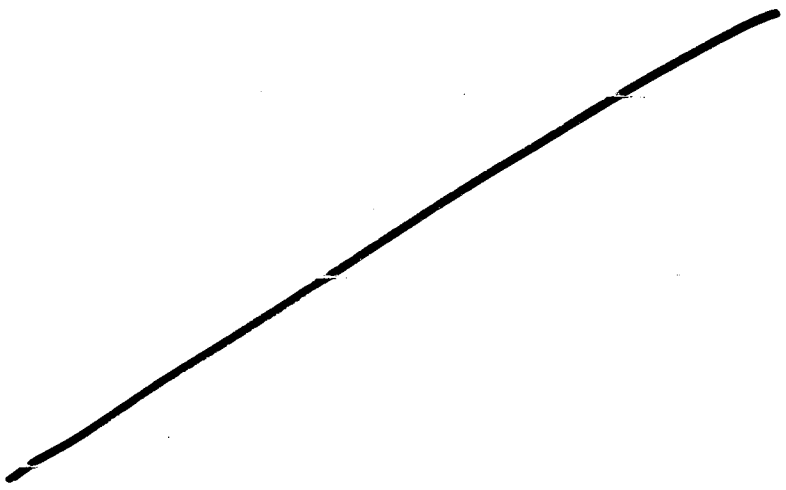
We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

1.

2.

3.

4.



b(4)

5. [redacted] b(4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
5/21/2008 04:46:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-285

UCB, Inc.
Attention: Linda Noa, M.S., RAC
Regulatory Affairs Manager
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Noa:

Please refer to your new drug application (NDA) dated November 13, 2007, received November 14, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Keppra XR™ (levetiracetam) Extended-Release Tablets, 500 mg.

We also refer to your submission dated November 29, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 14, 2008.

We request that you submit the following information:

Chemistry

With regard to the proposed specification for Keppra XR Tablets, you have not provided any data to support the suitability of the proposed dissolution/drug release method. The following information is needed to assess the adequacy of the method for quality control purposes:

1. Provide a rationale, and supporting data as appropriate for the choice of dissolution apparatus, rotation speed, and dissolution media.

2. Provide data to demonstrate the ability of the method to discriminate between acceptable and unacceptable batches.

Clinical Pharmacology

Please provide the validation report for the HPLC method used for the plasma sample from clinical study N01235 that was analyzed by [redacted] b(4)

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients less than 12 years old.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
1/28/2008 06:16:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-285

NDA ACKNOWLEDGMENT

UCB, Inc.
Attention: Linda Noa, M.S., RAC
Regulatory Affairs Manager
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Noa:

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

Name of Drug Product: Keppra XR™ (levetiracetam) Extended-Release Tablets, 500 mg

Date of Application: November 13, 2007

Date of Receipt: November 14, 2007

Our Reference Number: NDA 22-285

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 12, 2008, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-

standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
12/19/2007 06:27:30 PM

FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time:	October 1, 2007
Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Location:	Videoconference
Application Number:	Pre-IND 73,703
Product Name:	Keppra (levetiracetam)
Received Briefing Package	August 31, 2007
Sponsor Name:	UCB, Inc.
Meeting Requestor:	Linda Noa
Meeting Chair:	Russell Katz, M.D.
Meeting Recorder:	Susan Daugherty
Meeting Attendees:	

FDA Attendees

Division of Neurology Products (DNP)
Russell Katz, M.D., Director
John Feeney III, M.D., Acting Deputy Director
Norman Hershkowitz, M.D., Ph.D., Medical Reviewer
Susan Daugherty, Regulatory Project Manager
Tina Kasliwal, Pharmacy Student Intern

Division of Pre-Marketing Assessment I
Martha Heimann, Ph.D., Pharmaceutical Assessment Lead

Division of Clinical Pharmacology I
Veneeta Tandon, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics II
Jingyu Luan, Ph.D., Biometrics Reviewer

External Attendees

UCB, Inc.
Patty Fritz, Vice President, Global Regulatory Affairs
Peter Verdru, Vice President, Clinical Research, Head of Neurology/Psychiatry Clinical Development
Armel Stockis, Head of Global Pharmacometrics
Sarah Lu, M.D., Ph.D., Clinical Program Director
Elisabeth Rouits, Clinical Pharmacometrics Specialist

Michel Boddaert, Global Statistical Team Leader
Benjamin Duncan, Associate Director, Biostatistics
Cecilia Dubois, Biostatistician CNS
Karen Campbell, Clinical Development Submissions Manager
Anthony Guichaux, Global Pharmaceutical and Analytical Development
Cassie Buckhalt, Regulatory Affairs CMC
Shannon Helms, Regulatory Operations Dossier Manager
Carol Bett, Regulatory Operations Dossier Manager
Linda Noa, Regulatory Affairs Manager

1.0 BACKGROUND

On April 19, 2006, a pre-IND meeting was held between the Division of Neurology Products and UCB, Inc. to discuss the development plan for levetiracetam extended-release tablets, 500 mg.

On July 27, 2007, a Pre-NDA meeting request was submitted to discuss the NDA submission for levetiracetam extended-release tablets. Responses to the questions contained in the briefing package were electronically mailed to the Sponsor on September 28, 2007.

Questions from the sponsor are not bolded or italicized. Responses from the FDA are in bold after each question. The meeting discussion is bolded and italicized.

2.0 DISCUSSION

1.1 Quality (CMC)

Question 1: Is the proposed quality information adequate for the filing and review of the NDA?

Preliminary FDA Response:

The proposed information is generally adequate; however, you will need to provide facility information for the sites involved in drug substance manufacturing, testing, etc. This information is used to request establishment evaluations from the CDER Office of Compliance. Also, we request that a summary table for the drug substance be provided. It is not necessary to resubmit drug substance specifications analytical procedures or method validation data that have been reviewed under NDA 21-035.

Consistent with the approved immediate release tablet specifications, the following tests for release are to be performed on the commercial (extended release) drug product:

- **Appearance (Visual)**
- **ID (HPLC**
- **Uniformity of Dosage Units by mass variation (** **, USP <905>)** b(4)
- **Drug Release (Dissolution** **, USP <724>):**
  1 hour:
  2 hour:
  4 hour:
  8 hour: b(4)
- **Assay**
- **Impurities –**

  Total Related Substances:
- **Impurities –**
- **Water Content** b(4)

Discussion:
The Division clarified that a drug substance specification table should be provided.

Question 2: Are the proposed NDA drug product tests and specifications acceptable to the Division?

Preliminary FDA Response:
The proposed tests appear appropriate for control of the proposed product. The adequacy of the analytical procedures and acceptance criteria will be evaluated during the NDA review.

There was no further discussion of the response to this question at the meeting.

Question 3: Is the proposal to satisfy the commitment, to place the first three commercial batches on stability, with data from the first three validation (full scale) batches acceptable to the Division?

Preliminary FDA Response:
Yes

There was no further discussion of the response to this question at the meeting.

1.2 *Nonclinical*

Question 4: Is the proposal to not include nonclinical information for the filing and review of the NDA acceptable to the Division?

Preliminary FDA Response:
Yes, unless non-clinical information is needed to support any proposed labeling changes.

There was no further discussion of the response to this question at the meeting.

1.3 *Clinical*

Question 5: Are the proposals for clinical information adequate for review and to support the proposed indication?

Preliminary FDA Response:
The information, as outlined, appears adequate. The population PK datasets must be submitted in SAS XPORT transport format, version 5.

There was no further discussion of the response to this question at the meeting.

Question 6: Is the plan for the population-pharmacokinetic meta-analysis acceptable to the Division?

Preliminary FDA Response:
Yes.

There was no further discussion of the response to this question at the meeting.

1.3.1 Integrated Summary of Safety (ISS):

Question 7: Is the plan for the ISS acceptable to the Division?

Preliminary FDA Response:
Yes. This should contain narratives of all deaths and serious adverse events as well as all discontinuations. Discontinuations because of loss of efficacy should

be separately analyzed and such narratives should be included. The ISS should also contain a comparison of discontinuations resulting from seizures (loss of efficacy) and a separate section describing these. A comparison with prior adjunctive studies at similar doses would be of interest, with the understanding that cross study comparisons of this nature must be interpreted with caution. ISS should contain all pertinent elements as described in the previous Appendix distributed to the Sponsor at the pediatric exclusivity pre-NDA meeting.

Discussion:
The Sponsor may cross reference previous adjunctive study submissions that contain data regarding loss of seizure control using the same doses as for the Keppra XR studies so long as the included discussion is cogent.

The Sponsor proposes to report adverse events with a cutoff at 2% for clinical studies and 5% for PK studies. This is acceptable to the Agency.

Regarding the Appendix A, "Elements to include in an ISS," that was included with the 9-17-07 meeting minutes for IND 45,151: the Agency clarified that the Sponsor may omit the sections that do not apply.

1.3.2 Integrated Summary of Efficacy (ISE):

Question 8: Is the plan to not include an ISE acceptable to the Division?

Preliminary FDA Response:
This is adequate, but it would be of interest if the study report contained a pharmacokinetic/pharmacodynamic comparison with previous adjunctive studies: i.e. does the efficacy appear similar at the same dose/exposure concentrations. It is understood that this cross study comparison must be interpreted with caution.

Discussion:
The Sponsor clarified that they will be conducting a descriptive exposure-response analysis in lieu of a PK-PD analysis. The Agency noted that this would be acceptable but they must explain any obvious differences.

1.3.3 120-day Safety Update:

Question 9: Is the plan for the 120-day Safety Update acceptable to the Division?

Preliminary FDA Response:
Yes.

There was no further discussion of the response to this question at the meeting.

1.4 Administrative

1.4.1 Electronic Submission

Question 10: Are the plans concerning the electronic submission and folder structure of the NDA acceptable to the Division?

Preliminary FDA Response:
We anticipate that the new policy requiring all applications to be in the eCTD format will be posted in the Federal Register and on the FDA web site by sometime this Fall. That policy will include directions for how to request waivers. If the submission is received after December 31, 2007, you will need to request a waiver.

Your proposed document mapping is acceptable for an electronic NDA in CTD format. However, cross references cannot be hyperlinked to other NDAs previously submitted and, therefore must be provided in text. PDF files must be version 1.4 per *Portable Document Format specifications*, found at http://www.fda.gov/cder/regulatory/ersr/ectd.htm.

There was no further discussion of the response to this question at the meeting.

1.4.2 Case Report Forms

Question 11: Is the plan for the submission of CRFs acceptable to the Division?

Preliminary FDA Response:
CRFs for serious adverse events should be included. Datasets must be delivered in SAS XPORT transport format v.5. SAS v. 9 is unacceptable. However, delivering SAS programs in ASCII and/or PDF formats is acceptable.

There was no further discussion of the response to this question at the meeting.

1.4.3 Case Report Tabulations and Related Files

Question 12: Is the proposed content of the domain and patient profiles adequate for the review of the NDA? Is the submission of the domain profiles and patient profiles in conjunction with the CRFs sufficient to meet the requirements? Are the datasets submitted in electronic format as SAS transport files acceptable for the archival copy of the application?

Preliminary FDA Response:
These appear adequate from a clinical perspective. In addition, the submission of the datasets in transport format is acceptable except all datasets must be submitted in SAS transport V5 format.

There was no further discussion of the response to this question at the meeting.

Question 13: Given the data provided herein and the currently proposed plans, would the

[redacted] b(4)

Preliminary FDA Response:
The key study will be a single dose fasted bioequivalence study between 2x750 mg versus 3x500 mg. Multiple dose BE study is not necessary. A food effect arm can be added to this study. We recommend that you submit the results of this study for further discussion [redacted] b(4)

Discussion:
The Agency clarified that the Sponsor should conduct single dose BE study with 2x750 mg tablets fasted, 3x500 mg tablets fasted and 2x750 mg fed arms. Should the equal doses of 500 mg and 750 mg tablets strengths not be bioequivalent, additional data may be needed, such as a clinical efficacy study.

Additional Clinical Pharmacology Comment:

An outline of the summary section of the Human pharmacokinetics and Biopharmaceutics data is provided (see Appendix A). At the time of NDA submission you may use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to us as a review aid. This summary can either be placed in Module 2 along with the clinical summary or can be provided as a review aid under Module 5.

Discussion:
The Sponsor may refer to previous submissions for certain sections (e.g., drug interactions) rather than recompiling all the data. They should include information from this submission where possible (e.g., intrinsic factors: age, gender race information from the meta analysis)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

Clinical Pharmacology Review Aid

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

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Russell Katz
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 19, 2006

From: Katherine Needleman, M.S., DNP, HFD-120

To: UCB, Inc.

Subject: Pre-IND 73,703 Meeting Summary

Meeting Date: April 19, 2006 **Time: 11:00 AM - 12:00 PM**

Location: White Oak, Conference Room 1313

Meeting Requestor/Sponsor: UCB, Inc.

Product: Levetiracetam (Keppra)

Proposed Use: Treatment of epilepsy

Type of Meeting: Pre-IND

Meeting Purpose: To discuss the development plan for Levetiracetam extended release tablet 500 mg

Sponsor question and FDA response:

Note: Draft responses by FDA were emailed to UCB, Inc. on April 17, 2006. Below contains the emailed response followed by discussion at the meeting.

Meeting Summary

Question 1: Is the drug product stability program to support the proposed 24 month expiry for the commercial presentation (red film-coated tablets debossed with "KEPPRA" on one side and "500 XR" on the other side) acceptable to the Division?

Agency Response: The proposed stability package, i.e., 12 months long-term data for three pilot scale batches of — tablets and 6 months data for one batch of market image (red) tablets is acceptable. Testing on market image tablets should include photostability studies. The expiration dating period assigned during the review will depend on the data. b(4)

Discussion During Meeting: UCB stated photostability will be performed as well as the effect of alcohol on *in vitro* dissolution.

Question 2: Are the plans for comparative dissolution between the clinical tablets and the proposed commercial tablets acceptable to the Division?

Agency Response: Yes

Discussion During Meeting: No comments made.

Question 3: Is the proposed NDA drug product specification acceptable to the Division?

Agency Response: The proposed testing appears acceptable. Adequacy of the acceptance criteria will be determined during the review.

Discussion During Meeting: No comments made.

Question 4: Is the proposal to satisfy the commitment to place the first three commercial batches on stability with data from the first three validation (full scale) batches acceptable to the Division?

Agency Response: Yes

Discussion During Meeting: No comments made.

Question 5: Is the plan to maintain the use of ——— with a commitment to perform the periodic testing, as approved for — tablets, acceptable to the Division? b(4)
Clarifying Note: ——————— for manufacture of immediate release Keppra (levetiracetam) Tablets (NDA 21-035/S-048).

Agency Response: Yes

Discussion During Meeting: No comments made.

Question 6: Based on the extensive nonclinical data in support of the approved KEPPRA immediate release tablets and the commonly used excipients in the extended release formulation, is the plan to not conduct additional nonclinical studies acceptable to the Division?

Agency Response: Yes, provided there are no new impurities or degradants in the ER formulation that are of particular concern (i.e., genotoxic) or that exceed the qualification threshold (cf. Guidance for Industry Q3A Impurities in New Drug Substances February 2003 ICH; Guidance for Industry Q3B(R) Impurities in New Drug Products November 2003 ICH Revision 1).

Discussion During Meeting: UCB stated there have been no new impurities or degradants observed.

Question 7: Is the plan for the collection of clinical pharmacology data and the design of the single and multiple dose bioequivalence and food effect study acceptable to the Division?

Agency Response: Yes.

Comment on Study N01160: The sponsor should also calculate the 90% CI for Cmin values for the multiple dose comparative BE section of the study.

Discussion During Meeting: UCB proposed the following modifications to the PK/BE Study N01160: To add Cmin 90% CI at steady-state, to add T75%Cmax at steady-state, and to add PK dose proportionality testing. FDA stated this was acceptable however; UCB may be able to get information on dose proportionality from the clinical trial as well if they add 2000 and 3000 mg doses in the clinical trial and if adequate PK sampling is conducted.

Question 8: Is the design of the efficacy and safety study acceptable to the Division?

Agency Response: The design is generally acceptable. An argument could be made that if pharmacokinetic bioequivalence is demonstrated, this safety/efficacy study may be unnecessary. The division invites the Sponsor to present an argument that will justify approval based upon pharmacokinetic equivalence. The argument should include, but should not be limited to, the following points.

- The Sponsor should present an argument as to why therapeutic efficacy and safety should be determinable by the point concentrations, Cmax and Cmin, and AUC equivalence. Such an argument would require an understanding of the PK/PD relationship for the drug. In the past, some sponsors have investigated this relationship in animal models of epilepsy. The division is concerned that the therapeutic effect may be dependent upon rate of change in concentration.

- As noted above Cmin will also have to be examined. The Sponsor should examine whether Cmin for the ER compound is equivalent and/or greater than for the reference IR compound.

- If point concentration is an adequate determination of therapeutic efficacy and safety equivalence between reference and test compounds it may be important to examine the actual time spent at various concentration ranges as measured by chronic dosing PK studies.

If the PK study alone is determined to be inadequate the division has the following comments on the submitted protocol. The present protocol examines one low dosage in the complete study population despite the fact that the label presently recommends different mg/kg pediatric dosing between adults and children because of the greater clearance in children (see above recommended doses in introduction). According to the label, children 6-12 exhibit 40% higher clearance then adults. The prior pediatric study targeted a dose of 60mg/kg, which in a >40 kg patient was estimated as 3,000 mg/day. Some flexibility was allowed with a mean dose of 52 mg/kg being achieved. The present study includes children >12 years of age. The original pediatric study did not appear to examine a fixed 1000 mg/day dose in this age group of patients as did the adult studies. Children may therefore be under-dosed.

As Keppra is presently labeled for 1,000 to 3,000 daily in adults, and assuming that a PK study alone is inadequate, all dosages should be examined in the present study.

There is no specification as to whether drug is to be administered under fed or non-fed conditions. If bioavailability demonstrates a food effect this will presumably be changed.

The sponsor intends to evaluate leveritacetam concentrations in patients in this study. However, no details of sampling times and analyses plan have been included in the protocol. The sponsor should include this information in the protocol.

Discussion During Meeting: UCB explained the criteria for the BE approach as follows:

- Well-characterized PK/PD relationship

- Data to confirm the relationship between the therapeutic effect and the rate of change in concentration

- Cmin for ER compound equivalent and/or greater than reference IR compound

- Data to demonstrate that point concentration is an adequate determination of therapeutic efficacy and safety equivalence between reference and test compounds

Therefore, UCB's conclusion was that Study N01235 is essential for approval with the following modifications because they do not have data to support a well characterized PK-PD relationship and the importance of the rate of change of concentration on efficacy and safety.

The Sponsor, therefore, proposes a study that includes the following elements:

- Include all labeled doses
  - forced titration up to 3000 mg/day (1000 mg/day for 4 wks, 2000 mg/day for 4 wks, 3000 mg/day for 4 wks)
- Population PK analysis includes sampling at each dose level
- Change from one-sided test to two-sided test and power reduced to 85% to maintain similar sample size
- Primary efficacy analysis will combine all three dosing periods (exploratory analysis will be done to compare the three dosing periods)
- Examine Cmin analysis with a 90% confidence interval evaluation

Regarding age, UCB stated the current label suggests children weighing 50 kg and above should be dosed as adults. Therefore, only pediatric patients weighing > 50 Kg will be studied. Regarding food, UCB stated study N01140 suggests no significant food effect.

FDA stated UCB's proposal is acceptable and FDA appreciated the honest look at their data. FDA questioned the practicality and ethics of performing the study in countries where Keppra is not commercially available. UCB explained feasibility trials were performed and they have found several countries where they believe this will be feasible (e.g., Brazil, Russia, South Africa, India and Poland). These countries either have the drug available and the drug is not on the reimbursement list or have a generic available. Patients who participate in the trial and show a benefit will be allowed to continue treatment following the study. [redacted] b(4)

The division asked, given the revised plan, if UCB has considered studying several fixed doses rather than a forced titration. A dose-response would be useful to learn the correct dose so as not to use a higher dose than necessary. UCB stated they did consider this, but it would be a placebo-controlled 4-arm study and would take a long time to complete. They would also need a very large sample size to show a dose-response effect in the study. FDA then posed the question if UCB has considered a single fixed dose but at a lower dose. As currently designed, the study would impose the drug to be labeled at 3000 mg. If 1000 mg is as good as 3000mg, why study the

higher dose? Following a discussion on the dose effect, it was concluded that the clinical study will be performed at 1000 mg and the PK study will go up to 3000 mg. This would allow the label to include a dose up to 3000 mg (as long as all BE criteria are met, there is dose proportionality and Cmin matches). The sponsor should provide 90% confidence intervals using the dose-normalized PK parameters in the dose proportionality study.

Question 9: Is the analysis using [redacted] *acceptable to the Division?* b(4)

Agency Response: The agency's standard is to use a two-side test at 5% significance level. The proposed [redacted] b(4)

Discussion During Meeting: See above. UCB agreed to use a two-sided test and power reduced to 85% to maintain similar sample size.

Question 10: Is the overall development plan and data to be provided sufficient for the approval of the levetiracetam extended release tablet?

Agency Response: Yes, with issues raised above and below in mind.

Discussion During Meeting: See comments above and below.

Question 11: Does the development plan, including the planned efficacy and safety study, meet the regulatory requirements for obtaining 3 years marketing exclusivity for the levetiracetam extended release tablet?

Agency Response: It is premature at this time to respond to this question.

Discussion During Meeting: UCB asked for clarification. FDA stated that at the time, it was not known if UCB would be pursing a clinical or BE approach and also cannot assume what will be on the market at time of approval. FDA stated that if no other marketed product is available with this indication, and clinical data is submitted and if the rules of Waxman Hatch are met, exclusivity should be granted.

Question 12: Given the demonstration of bioequivalence in study N01160 and the demonstration of efficacy and safety in study N01235, would it be acceptable to the Division to incorporate all the approved indications for KEPPRA in the labeling for the levetiracetam extended release tablet, for adults and adolescents [redacted] years of age and older? b(4)

Agency Response: If bioequivalence alone is sufficient no additional studies in individual seizure disorders would be necessary. If it is insufficient, testing in seizure disorders other then partial would be required.

Discussion During Meeting: UCB commented that regarding other seizure types, UCB proposes to limit the indication to epilepsy of partial origin. UCB acknowledged that another clinical study will be needed to label the drug for other indications, but due to the difficult in recruiting, UCB does not plan to pursue other indications at this time.

Question 13: Given the demonstration of bioequivalence for twice daily dosing of the approved levetiracetam immediate release 500 mg tablet (1000 mg/day) and once daily dosing of 1000 mg for the levetiracetam extended release tablet (2 x 500 mg), would it be acceptable to the Division for the levetiracetam extended release tablet to be labeled for the daily dose range of 1000 mg to 3000 mg approved for KEPPRA?

Agency Response: If PK alone is sufficient the sponsor need not perform higher dose BE studies but will have to provide dose proportionality data for 1000-3000 mg doses. The sponsor should also consider developing higher strengths of the ER dosage form in order to avoid the administration of multiple units (4-6 to achieve the 2000 and 3000 mg doses). If the sponsor does plan on developing higher strengths, then a dosage form bioequivalence study can be conducted in lieu of the dose proportionality study in order to cover the proposed dose range for labeling.

If PK studies are insufficient the Sponsor will be required to perform studies at all labeled doses.

Discussion During Meeting: See discussions above.

At the end of the meeting discussions the final approach regarding their development plan that UCB discussed was that they would conduct a single and multiple dose BE study with the 1000 mg, efficacy study with the 1000 mg and a dose proportionality study with 1000, 2000 and 3000 mg (this dose proportionality study may either be a stand alone study or will be combined with the single dose BE study). FDA agreed to this approach.

Additional Clinical Pharmacology Comment:

Dose dumping with alcohol should be evaluated. First in vitro dissolution studies in various concentrations of alcohol (e.g., 5, 10, 20 and 40%) should be conducted. Once results are available, the sponsor should discuss this with the Office of Clinical Pharmacology for assessing the need for in vivo study.

Discussion During Meeting: The sponsor agreed to do this.

FDA Attendees: Russell Katz, John Feeney, Norman Hershkowitz, Ramana Uppoor, Veneeta Tandon, Kevin Cannard, Ed Fisher, Kun Jin, Katherine Needleman
Students: Ammar Itusan, Jeannettee Joyner, Alia McConnell

Sponsor Attendees: Patty Fritz, Sandy Bonsall, Zhihong Lu, Armel Stockis, Anita Fauchier, Peter Verdru, Remy von Frenckell, Caroline Goffin, Domenico Fanara, Yee Kan, Linda Noa

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/s/

Russell Katz
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