

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205836Orig1s000

205837Orig1s000

205838Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA #: NDA 205836 (oral tablets), NDA 205837 (injection 10 mg/mL)

NDA 205838 (oral solution 10 mg/mL)

SUPPL #

HFD #

Trade Name: BRIVIACT

Generic Name: BRIVIACT (brivaracetam); 10, 25, 50, 75, and 100 mg oral tablets; injection (10 mg/mL); and oral solution (10 mg/mL)

Applicant Name: UCB, Inc.

Approval Date, If Known: February 19, 2016

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 X

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 X

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 X NO
New moiety exclusivity requested

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
Applicant did not specify. However, it is assumed that 5 years is requested.

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

YES NO X

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

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

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

YES NO X

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 X

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

NDA#

NDA#

NDA#

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:

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"):

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

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

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

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

(b) For each investigation not carried out under an IND or for which the applicant was

not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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: Cathleen Michaloski, BSN, MPH, RAC
Title: Senior Regulatory Project Manager
Date: 2.17.16; 2.22.16

Name of Office/Division Director signing form: Ellis F. Unger, MD
Title: Office Director, ODE I

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

/s/

CATHLEEN B MICHALOSKI
02/22/2016

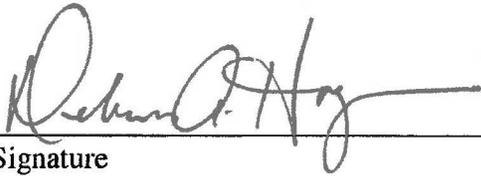
ELLIS F UNGER
02/23/2016



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.

 17 OCT 2014
Signature Date

Deborah Hogerman
Vice President, Regulatory Affairs North America
UCB, Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205836 NDA # 205837 NDA # 205838 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: BRIVIACT Established/Proper Name: brivaracetam Dosage Form: Tablets, oral: 10, 25, 50, 75 and 100 mg Oral Solution: 10 mg/mL Injection: 50 mg/5mL		Applicant: UCB, Inc. Agent for Applicant (if applicable):
RPM: Cathleen Michaloski		Division: DNP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is February 20, 2016 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority

Chemical classification (new NDAs only):

(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

REMS: MedGuide

- Communication Plan
- ETASU
- MedGuide w/o REMS
- REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 2.19.16
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	X Included
• Original applicant-proposed labeling	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	X Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	X Included
• Original applicant-proposed labeling	X Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	X Included
❖ Proprietary Name	Acceptable Letter 2/27/15 Review 2/22/15
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: X 1.29.15 None DMEPA: X 6/25/15 None DMPP/PLT (DRISK): X 6.25.15 None OPDP: X 12/23/15 None SEALD: <input type="checkbox"/> None X CSS: X None Product Quality X 12.16.15 None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	1/15/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	X Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes X No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>11.28.15 review ; meetings: 9/30/13, 11/18/15</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	X N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>) 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>) 	Included
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	Included
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	X N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 7/29/14
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 12/11/06
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 4/27/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 8/13/15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	X No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 2.19.16
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 2.19.16
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 2.18.16
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None 2.18.16
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews 	

<ul style="list-style-type: none"> • Clinical Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> 2.18.16
<ul style="list-style-type: none"> • Clinical review(s) <i>(indicate date for each review)</i> 	1/14/16
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	1/14/16 and 2.17.16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None Pediatrics review 11/28/15 IV safety review 10/19/15 Co admin w/ Oral contraceptive Review 8.17.16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input type="checkbox"/> N/A MR 3.12.15 DEA - TBD
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	2.22.16 (no REMS except MG) <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input type="checkbox"/> None requested 6.11.15
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	11.14.15
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 11.14.15
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8.26.15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	No separate review 8.31.15
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 8.31.15
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7.24.15, 8.31.15
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 1.23.16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12.2.15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc 9.17.15
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 9.4.15 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12.16.15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12.16.15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None Micro 12.16.15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	12.16.15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	12.15.16
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	12.15.16
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: 12.16.15 E. Dobbin <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Tuesday, February 02, 2016 6:05 PM
To: Kristen.Piatak@ucb.com
Subject: IR 205836, 7 & 8 Briviact labeling

Importance: High

Kristen,
we have the following information request from the clinical / safety reviewer:

Regarding your changes to Section 5.3, please justify your numbers of patients with non-psychotic and psychotic symptoms of (b) (4) % for BRIVIACT vs (b) (4) % for placebo. Our percentages reflected subjects with TEAEs in the SOC Psychiatric disorders. Please also justify your number of (b) (4)

Please respond by noon tomorrow.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
Bldg. 22, Room 4342
10903 New Hampshire Ave
Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov
301-796-1123*

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/s/

CATHLEEN B MICHALOSKI
02/03/2016

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, January 28, 2016 9:55 AM
To: Kristen.Piatak@ucb.com
Subject: Carton Labeling- NDA-205838 IR

Importance: High

Good Morning Kristen,
We have a comment/recommendation from our Drug Promotion review staff.

OPDP is concerned that the prominence and disparate font styles of the established name and proprietary name in the presentations on the carton and container labeling do not meet the regulatory requirements. Therefore, OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, “[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.”

Please address this concern and respond as soon as you are able, but no later than 2/2/16.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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CATHLEEN B MICHALOSKI
01/28/2016

**PeRC Meeting Minutes
November 18, 2015**

PeRC Members Attending:

Lynne Yao

Hari Cheryl Sachs

Linda Lewis

Lily Mulugeta

Thomas Smith

Shrikant Pagay

Daiva Shetty

Meshaun Payne

George Greeley

Gregory Reaman

Peter Starke (Non Responsive

Kevin Krudys

Julia Pinto

Dianne Murphy

Andrew Mulberg

Ruthie Davi

Diane Murphy

Barbara Buch

Lisa Faulcon

Adrienne Hornatko-Munoz (Non Responsive

Michelle Roth-Kline

Rosemary Addy

Agenda

NON RESPONSIVE

8:40	NDA 205836, 205837, 205838	BRIVIACT (brivaracetam) IV & Oral Solution (Partial Waiver/Deferral Plan with Agreed iPSP)	DNP	Cathleen Michaloski	Adjunctive treatment of partial onset seizures in patients 16 years of age and older with epilepsy
------	-------------------------------------	--	-----	------------------------	--

NON RESPONSIVE

1 Page(s) has been Withheld in Full Non-Responsive immediately following this page

NON RESPONSIVE

BRIVIACT (Partial Waiver/Deferral/Plan) with Agreed iPSP

- Indication: Adjunctive treatment of partial onset seizures in patients 16 years of age and older with epilepsy

- [Redacted] (b) (4)

The division also agrees with the sponsor's plan for partial waiver in patients below 1 month of age because a diagnosis cannot be reliably made in patients less than 1 month of age

- [Redacted] (b) (4)

- *PeRC Recommendations:*

- PeRC agreed with the division's plan to waive studies in pediatric patients from birth to <1 month of age because studies are impossible or highly impractical.

- [REDACTED] (b) (4) should be noted in the Division memo and in documents related to this iPSP as well as other iPSPs for other products for this indication.
- The PeRC recommended the timeline be updated to include specific dates.

NON RESPONSIVE

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/s/

MESHAUN L PAYNE
12/10/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Tuesday, October 27, 2015 11:45 AM
To: Kristen.Piatak@ucb.com
Subject: Brivaracetam Information Request - labeling- on Figure 1 histogram and sample size

Importance: High

Dear Kristen,

We have an information request from the clinical team:

1. The review team has concluded that in figure 1 section 14 the seizure response category histogram should be based on the full population, (b) (4) Please provide a revised histogram that includes all mITT patients, (b) (4) Also include the Section 14 narrative that will be included in the label describing the histogram.

2. In reference to sentence 1 of section 14, the population is noted to be (b) (4) patients. The efficacy population count identified by the review team based on a count of the mITT (study 1253) and ITT populations (study 1252, 1358) is 1550 patients. We request that you reconcile this (b) (4) patient difference in the size of the efficacy population.

Please respond by COB Friday Oct 30.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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301-796-1123*

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/s/

CATHLEEN B MICHALOSKI
11/06/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Wednesday, October 07, 2015 2:44 PM
To: [REDACTED] (b) (4)
Cc: deborah.hogerman@ucb.com
Subject: Information request- brivaracetam NDAs

Good Afternoon,

We have been reviewing the pediatric information in the applications and preparing for PeRC meeting next month. We note that you did not include a statement regarding certification for the waiver and deferral of the studies.

Please submit an amendment to the NDAs which certifies that all the information is true and correct and that it adequately supports the request for deferral /waiver of the required pediatric studies.

Example:

Pursuant to section 505B(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act applicant hereby certifies that the necessary pediatric studies in subjects agedXX- YY should be deferred/waived.

A separate statement is needed for the waiver and deferral you must site the reason the studies cannot be done (waiver).

One document addressing both is sufficient. Please have the document officially signed.

Submit this information within 2 weeks, by Oct. 21, 2015.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
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/s/

CATHLEEN B MICHALOSKI
10/07/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Tuesday, September 15, 2015 2:46 PM
To: Kristen.Piatak@ucb.com
Subject: Briviact information request -clinical safety

Hello Kristen,
We have an information request from our clinical safety reviewer:

In reference to NDAs 205836, 205837, 205838, please submit the following by COB September 18, 2015:

1. Please explain why the number of subjects with TEAEs for Pool S1 using the datasets sent in the Safety Information Amendment 8/31/15 is different from the numbers reported in Table 5.2.1.1.1 in Safety Information Amendment 8/11/15.

2. Using the updated datasets, please submit updated information for any additional pregnancies, neoplasms, overdoses (Safety Information Amendment 6/29/15 Table 1), and adverse drug reactions for labeling (ISS Table 6-26). If there are no changes in the data using the updated datasets, please state that there is no change.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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/s/

CATHLEEN B MICHALOSKI
09/15/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Friday, September 04, 2015 8:50 AM
To: deborah.hogerman@ucb.com
Cc: Kristen.Piatak@ucb.com
Subject: brivaracetam IR- clinical safety

Importance: High

Good Morning Deborah,
We have a clinical safety information request. In reference to NDAs 205836, 205837, 205838, please submit the following by COB September 8, 2015:

Please explain why the number of subjects with TEAEs (e.g., serious TEAEs in Pool S1 for placebo and the BRV 100 mg/day dose group) tabulated in the Safety Information Amendment dated 8/11/15 are lower than the values reported in the original ISS Tables.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
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/s/

CATHLEEN B MICHALOSKI
09/09/2015

Executive CAC

Date of Meeting: August 25, 2015

Committee: Abigail Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
David Joseph, Ph.D., DGIEP, Alternate Member
Ed Fisher, Ph.D., DNP, Presenting Reviewer and Acting Supervisor

Author of Draft: Ed Fisher

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 205836
Drug Name: Brivaracetam
Sponsor: UCB Pharma

Mouse Carcinogenicity Study

Brivaracetam was administered orally (diet + gavage, 5 mL/kg, BID) to mice (CrI:CD1(ICR), 60/sex/grp + 8 [C] or 18/sex/group TK) at total daily doses of 0 (1% w/v methylcellulose vehicle), 400, 550, or 700 mg/kg/day for 104 weeks. Dose selection was based on the results of a 13-week oral (gavage) study in CD-1 mice (see Exec-CAC minutes). The sponsor originally proposed total doses of (b) (4), and (b) (4) mg/kg/day in males, and (b) (4) and (b) (4) mg/kg/day in females. The Exec-CAC considered the highest doses too high based on deaths in the 13-week study and recommended total daily doses of 0, 125, 250, and 500 mg/kg/day.

Bodyweight (BW) gain over the treatment period was decreased in all treated groups (-32, -42, and -24% in males; -34, -21, and -24% in females at LD, MD, and HD; statistically significant (SS) in males at all doses and in LD females), but there was no dose relationship. At the end of the treatment period, mean BW was SS lower in LD and MD males and in LD female. There were no effects of treatment on survival or hematology parameters.

In the sponsor's analysis, the incidence of hepatocellular adenoma or carcinoma showed a SS trend and the incidence of hepatocellular adenoma was greater (SS) than controls in MD ($p < 0.05$) and HD ($p < 0.01$) males. Hepatocellular carcinoma was only seen in treated animals, with a SS difference from C in HD males. The incidence of hepatocellular carcinomas in LD and MD males was greater than C, but within the historical control range. There was no evidence of an increased incidence of hepatocellular tumors in females. There was a trend for increased incidences of benign luteoma and Sertoli cell tumors in treated females, but group differences did not reach SS. According to the sponsor, these findings should be considered of limited biological importance given the absence of other significant alterations in the female reproductive tract. There was no evidence of an effect of treatment on other tumor types.

The FDA statistical reviewer found SS ($p < 0.001$) dose response relationships in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma or carcinoma in male mice (**Table 1**). In female mice, the incidence of benign Sertoli cell tumor in ovaries also showed a SS dose response relationship. The pairwise comparisons showed SS ($p < 0.01$) increased incidences of hepatocellular adenoma and of carcinoma in males at the HD and a SS ($p < 0.01$) increased combined incidence of hepatocellular adenoma or carcinoma at the MD and HD in males.

Table 1. Incidences of liver tumors in male mice

Sex	Organ	Tumor Type	Group (N)				P_Value			
			C	LD	MD	HD	Dose Resp	C vs. L	C vs. M	C vs. H
Male	LIVER	HEPATOCELLULAR ADENOMA	7	9	16	17	<0.001*	0.3368	0.0118	0.0025*
		HEPATOCELLULAR CARCINOMA	0	2	3	9	<0.001*	0.2359	0.1083	<0.001*
		HEPATOCELLULAR ADEN+CARC	7	9	17	18	<0.001*	0.3368	0.0078*	0.0016*

Rat Carcinogenicity Study

Brivaracetam was administered orally (diet + gavage, 5 mL/kg, BID) to rats (Han Wistar, 50/sex/grp + 5 [C] or 10/sex/group TK) at total daily doses of 0 (C: 1% w/v methylcellulose vehicle), 150 (LD), 230 (MD), 450 (MHD), or 700 (HD) mg/kg/day for 104 weeks. In treated groups, the dose given by dietary admix was 100 mg/kg/day and doses administered by gavage were 50, 130, 350, and 600 mg/kg/day, split into two equal daily doses given 6 hours apart. Doses were based on the results of a 26-week toxicity study in Wistar rats. The Exec-CAC agreed with the 4 doses proposed by the sponsor in females (0, 150, 230, 450, and 700 mg/kg/day) based on MTD (lethality), but recommended administration of only the lower 3 doses in males (0, 150, 230, and 450 mg/kg/day).

There was no clear effect of treatment on survival, although the number of rats found dead was increased slightly in HD males and females. There were no notable clinical signs that could be attributed to treatment. In males, BW was SS lower (compared to C) from week 5 through to the end of the treatment period at all but the MD, and BW gain was lower (SS) in all treated groups over the treatment period, although the differences were not clearly dose related. In females, BW and BW gain were lower than controls in all treatment groups from week 3 until the end of the treatment period, but the differences were again not dose related. There were no effects on hematology parameters that were considered to be drug related.

In the sponsor's analysis, there was a SS trend for increased incidence of benign or malignant thymoma in females and a SS difference from C at the HD. The historical control range for this tumor was 0.0–8.7 %.

In the FDA statistician's review, the analysis showed SS ($p < 0.001$) dose response relationships for the incidence of benign thymoma and combined incidences of benign or malignant thymoma in the thymus of female rats and the pairwise comparison showed SS ($p < 0.01$) increased incidences of benign thymoma and combined benign or malignant thymoma (same incidence as benign except one additional LD) in the thymus in HD females compared to C (**Table 2**).

Table 2. Incidences of thymus tumors in female rats

Sex	Organ	Tumor Type	Group (N)					P-Value				
			C 50	LD 50	MD 50	MHD 50	HD 50	Dos Resp	C vs. L	C vs. M	C vs MHD	C vs. H
Female	THYMUS	BENIGN THYMOMA	2	2	4	5	11	<0.001*	0.6834	0.3178	0.1908	0.0049*
		THYMOMA_BEN + MALG	2	3	4	5	11	<0.001*	0.4897	0.3178	0.1908	0.0049*

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was adequate.
- The Committee concurred that increases in the following neoplasms were drug-related: hepatocellular adenoma in high dose males, hepatocellular carcinoma in high dose males, and adenoma or carcinoma (combined) in mid and high dose males.

Rat:

- The Committee concurred that the study was adequate.
- The Committee concurred that increases in benign thymoma and benign or malignant thymoma (combined) in high dose females were drug related.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

/Division File, DNP
/LFreed, DNP
/EFisher, DNP
/CMichaloski, DNP
/ASEifried, OND-IO

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/s/

ADELE S SEIFRIED
09/04/2015

ABIGAIL C JACOBS
09/04/2015



NDA 205836
NDA 205837
NDA 205838

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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

Attention: Deborah Hogerman
Vice President, Regulatory Affairs

Dear Ms. Hogerman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: BRIVIACT (brivaracetam); 10, 25, 50, 75, and 100 mg oral tablets;
injection (10 mg/mL); and oral solution (10 mg/mL)

We consider your August 11, 2015, submission to be a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 20, 2016.

If you have any questions, contact Cathy Michaloski, Sr. Regulatory Project Manager, by email at cathleen.michaloski@fda.hhs.gov or by phone (301) 796-1123.

Sincerely,

{See appended electronic signature page}

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

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/s/

WILLIAM H Dunn
08/20/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Friday, August 14, 2015 4:57 PM
To: deborah.hogerman@ucb.com
Subject: IR - SPL - Briviact (brivaracetam) NDAs 205836/205837/205838

Importance: High

Good Afternoon,

The SPL data elements portion of the label could not be located in the application. Please indicate where these can be found in the application, otherwise provide the SPL data elements (this is the section at the end of the SPL/xml document).

Please provide information to us by August 21, 2015.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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CATHLEEN B MICHALOSKI
08/14/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, August 06, 2015 10:17 AM
To: Michaloski, Cathleen

Importance: High

From: Michaloski, Cathleen
Sent: Thursday, August 06, 2015 10:14 AM
To: 'deborah.hogerman@ucb.com'
Subject: 8.6.15- 205836, 7, 8 Brivaracetam information request- clinical safety
Importance: High

Good Morning Deborah,

We have a request from our safety reviewer:

In reference to NDAs 205836, 205837, 205838, please submit the following by COB August 14, 2015:

The number of subjects with TEAEs reported in the CSRs for studies N01252, N01253, and N01358 do not match up with the total numbers for Pool S1 in the revised table submitted in the Safety Information Amendment on 7/9/15.

Please explain and/or clarify.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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/s/

CATHLEEN B MICHALOSKI
08/06/2015

Michaloski, Cathleen

From: Michaloski, Cathleen

Sent: Wednesday, August 05, 2015 3:02 PM

To: deborah.hogerman@ucb.com

Subject: 8.5.15- 205836, 7, 8 Brivaracetam comment for clarification - clinical safety

Good Afternoon Deborah,

we refer to the late cycle meeting discussion and previous IR's regarding the pending revised datasets.

In reference to NDAs 205836, 205837, 205838, the revised datasets (both ISS and 120-day Safety Update datasets) should include the same variables as the original datasets and the algorithms provided in the original submission ("algorithm-iss") and for the 120-day Safety Update ("algorithm-120day") should apply to these revised datasets.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

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10903 New Hampshire Ave

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Cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI
08/05/2015

From: Michaloski, Cathleen
Sent: Tuesday, August 04, 2015 6:40 PM
To: deborah.hogerman@ucb.com
Cc: Kristen.Piatak@ucb.com
Subject: 205836, 7, 8 Brivaracetam information requests - clinical safety
Importance: High

Good evening Deborah,

We have information requests from our clinical safety reviewer.

In reference to NDAs 205836, 205827, 205838, please submit the following by COB August 14, 2015:

1. CIOMS form for subject N01306-090-K033 (SAE renal failure acute). The narrative for this subject does not report a kidney biopsy. However, in the ISS, it is reported on page 456, that the subject underwent a kidney biopsy that revealed "chronic tubule-interstitial disease." Please clarify.
2. Studies that assessed endocrinology parameters were listed in the ISS. However, the results of these endocrine assessments (e.g., TSH, T3, T4) were not included in some of the respective clinical study reports. Please provide an integrated analysis of all of the endocrine laboratory parameters (i.e., TSH, TEAEs, T4, FSH, LH).

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

DNP/ODE I/OND/CDER

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10903 New Hampshire Ave
Silver Spring, MD 20993*

Cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI
08/04/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, July 23, 2015 4:24 PM
To: deborah.hogerman@ucb.com; Elena.Cleary@ucb.com
Cc: Kristen.Piatak@ucb.com
Subject: N 205836, 7, 8 IR safety clinical information request

Importance: High

Good Afternoon,
we have an information request from our safety reviewer:

In reference to NDAs 205836, 205827, 205838, please submit the following by **COB July 31, 2015:**

- 1) Narratives for the pregnancies (along with type of contraception used and concomitant medications) in subjects N01252-140-B173, N01358-038-00665, N01263-603-01772, N01358-411-00929, and N01358-130-00064.
- 2) Please submit a list of the actual quantitative ECG parameters (from the actual ECGs) for all subjects with ECGs reported as abnormal and clinically significant on the CRF in Pool S1 (stratified by randomized treatment group).
- 3) Please fill in the table below and submit separate tables for systolic blood pressure and another for diastolic blood pressure for Pool S1.

Table 1 - Decrease from Baseline in Blood Pressure, Pool S1

	Placebo	BRV 50 mg	BRV 100 mg	BRV 200 mg	BRV ≥50 mg
First 7 days	n=459	n=200	n=353	n=250	N=803
Decrease 5 - 10 mm Hg					
Decrease 11 - 15 mm Hg					
Decrease 16 - 20 mm Hg					
Decrease > 20 mm Hg					
Decrease > 40 mm Hg					
Week X (with separate rows for Week 2, 4, 8, 12, etc)	n=	n=	n=	n=	n=
Decrease 5 - 10 mm Hg					
Decrease 11 - 15 mm Hg					
Decrease 16 - 20 mm Hg					
Decrease > 20 mm Hg					
Decrease > 40 mm Hg					
End of Treatment	n=	n=	n=	n=	n=
Decrease 5 - 10 mm Hg					
Decrease 11 - 15 mm Hg					
Decrease 16 - 20 mm Hg					
Decrease > 20 mm Hg					
Decrease > 40 mm Hg					

Any question, do not hesitate to contact me. Thank you.

Cathleen Michaloski, BSN, MPH, RAC
Sr. Regulatory Project Manager

*Division of Neurology Products
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/s/

CATHLEEN B MICHALOSKI
07/23/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Tuesday, July 14, 2015 11:59 AM
To: Kristen.Piatak@ucb.com
Subject: Clinical /Statistical IR for 205836

Importance: High

Dear Kristen,

We have an information request from the clinical and statistical review staff for brivaracetam:

Please provide one dataset for each of the studies N01252, N01253 and N01358 for carbamazepine used as concomitant AED with the following information:

The dataset should have one record per patient for all patients included in the primary efficacy analysis. The following variables need to be included:

1. Subject ID (This variable will be used to merge with other datasets, so please use the same variable as used in the primary efficacy data: sbjnbr for N01252 and N01253; usubjid for N01358)
2. Whether or not carbamazepine was used as concomitant AED during the study.
3. Study day of the starting date (this could be negative if started prior to study entry; if the starting date prior to study entry is not available, use 1 instead).
4. Study day of the ending date.

Please provide the requested datasets as soon as possible or no later than noon Monday July 20, 2015.

As always, contact me if any questions. Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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Bldg. 22, Room 4342
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Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov
301-796-1123*

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/s/

CATHLEEN B MICHALOSKI
07/14/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Friday, June 26, 2015 12:51 PM
To: Kristen.Piatak@ucb.com
Subject: Briviact 205836, 7 & 8 carton and container labeling

Importance: High

Dear Kristen,

The medication error prevention and analysis (DMEPA) reviewer has the following recommendations:

We recommend the following be implemented prior to approval of the NDAs:

A. Container Labels (retail and professional sample)

1. For the professional sample blisters: We note that the blister card labeling for the 28 tablet professional samples state (b) (4). However, since the prescription samples are multi-unit blister packs that will be dispensed to the patient, revise the product strength to read "XX mg per tablet" to clarify the strength per unit and minimize the potential for wrong dose errors.

2. For the professional sample blisters: The proprietary and established name, strength, lot number, expiration date, (b) (4) and manufacturer should appear over each blister cell so that this important information remains available to the end user up to the point at which the last dose is removed. Revise the blister cell label to accommodate all critical information on each blister cell. If it is not possible to label each blister, a random display of the information can appear multiple times across the back of the blister.

3. For the injection: The last two digits of the NDC # on the vial container label should not be the same as the carton labeling of 10 units. Revise the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.

4. For the oral solution: We note the statement "Discard any unused (b) (4) (b) (4) remaining after 5 months of first opening the bottle" followed by "(b) (4) _____". To avoid use beyond 5 months of first opening the bottle we recommend that you replace the term "(b) (4) _____" with "Discard after _____."

5. We note that you propose a Medication Guide for your product, however, the statement "Dispense accompanying medication guide to each patient" (b) (4) _____ . Ensure that this statement is prominently displayed on the label for all strengths of the 60-count bottles. [see 21 CFR 208.24(d)]

B. Carton Labels (retail and professional sample)

1. For professional sample blister cartons: See A.1 above.
2. The injection carton labeling includes the route of administration in the upper right side of the principal display panel of the carton labeling, however, it lacks prominence. To minimize the potential for errors of wrong route of administration, relocate the statement, “ For Intravenous Use Only” away from the net quantity statement and with the statement of strength, in bold font, for example:

BRIVIACT

(brivaracetam) injection

50 mg/ 5 mL

(10 mg/ mL)

For Intravenous Use Only

3. We recommend revision of the net quantity for the hospital unit dose carton labeling to represent the packaging configuration, such as ‘100 tablets (4 X 25-count blister cards)’.

Thank you. As always, any questions do not hesitate to contact me.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

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/s/

CATHLEEN B MICHALOSKI
06/26/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Monday, June 22, 2015 9:43 AM
To: Kristen.Piatak@ucb.com
Subject: Clinical / safety IR for brivaracetam 205836, 7 & 8

Importance: High

Good Morning Kristen,

We continue our review of the NDAs. We have the following IR from the clinical safety reviewer:

In reference to NDAs 205836, 205827, 205838, please submit the following by COB June 29, 2015:

1. Please confirm that there were no subjects who met the Hy's Law laboratory criteria in the entire BRV development program (including all of the other supportive pooled groups).
2. Provide tables similar to ISS Table 5.11.10.1.1 for the Phase 1 pooled groups.
3. One subject in Pool S4 developed the TEAE of Drug rash with eosinophilia and systemic symptoms. This subject was not discussed in either the ISS or 120-day Safety Update. This TEAE was not listed or discussed in the subject's narrative provided in the ISS (an updated narrative was not provided in the 120-day Safety Update). Please explain. Please provide the subject's narrative with details regarding this TEAE.
4. Provide an analysis of HSS/DRESS for Pool Other.
5. For the BRV-treated subjects who discontinued due to TEAEs of pruritus, rash, urticaria, and drug hypersensitivity in Pool S4, provide an analysis of HSS/DRESS using actual relevant laboratory data and the vital sign of fever (rather than the MedDRA PT pyrexia). Categorize the subjects as definite, probable, or possible using the table provided in Kardaun SH et al. Br J Dermatol. 2007; 156(3): 609-11. Provide a similar analysis for SAEs and discontinuations due to TEAEs (in the SOC Skin and subcutaneous tissue disorders and SOC Immune system disorders) for all other pooled groups.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

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CATHLEEN B MICHALOSKI
06/22/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Monday, June 15, 2015 3:56 PM
To: Kristen.Piatak@ucb.com
Subject: clinical safety IR for 205836, 7 & 8

Importance: High

Hello Kristen,
we have another information request from the safety reviewer. Thank you.

In reference to NDAs 205836, 205827, 205838, please submit the following by COB June 19, 2015:

- 1) Please provide the outcomes for the pregnancies for subjects N01199-1003-0010 and N01379-480-00148.
- 2) In the information amendment dated 6/12/15, subject N01199-1082-0002 is listed in Table 1-2 as a subject who reported spontaneous or missed abortions. However, in ISS Table 9-13, the subject's outcome is reported as "two full term healthy babies." Please explain. Provide the following information: # of subjects (along with subject numbers) stratified by pregnancy outcome (healthy deliveries, spontaneous abortions, induced abortions, missed abortions, unknown outcome). Including the information provided in the 120-day Safety Update, the number of pregnancies should be 41 with 43 outcomes in 40 BRV-treated subjects. Please confirm.
- 3) In the information amendment dated 6/12/15, subject N01252-258-F182 is not listed in Table 1-2 as a subject who reported spontaneous or missed abortions even though in ISS Table 9-13, this subject is listed as having a spontaneous abortion as an outcome. Please explain. Please provide the past medical history and obstetric history for this subject.
- 4) For subjects N01253-355-B320, N01358-110-01045, N0199-1261-0003, please submit full CIOMS form (including information regarding the hospitalization).
- 5) For subject N01199-1051-0002, please provide more details regarding the TEAE leading to discontinuation coded to morbid thoughts.
- 6) For falls and injuries, in addition to the analyses provided in the ISS, provide the following analysis (using the table shell below – example for Pool S1) for Pool S1 and Pool S3. For falls, in addition to TEAEs of the PT of fall, include verbatim terms with "fell" or "fall". Provide a list of those verbatim terms with "fell" or "falls" that were not coded to the PT fall.

	Placebo		BRV	
	n (%)	total	n (%)	total
# subjects with falls		459		1099
# subjects with falls with concurrent seizure				
# subjects with falls without concurrent seizure				
# subjects with injuries		459		1099
# subjects with injuries with concurrent seizure				
# subjects with injuries without concurrent seizure				

Please respond by [June 19, 2015](#), and do not hesitate to contact me if any questions. Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

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CATHLEEN B MICHALOSKI
06/15/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Friday, June 12, 2015 12:24 PM
To: Kristen.Piatak@ucb.com
Subject: Brivaracetam clinical/safety IR 205836, 7 & 8; June 12, 2015

Importance: High

Good Afternoon Kristen,

In response to your email late yesterday, the clinical safety reviewer agrees that analyses of consecutive PCST laboratory results for ≥ 2 visits for Pool Phase 1, Pool iv, and Pool Other are not necessary.

The review team has another set of questions. Please see below:

In reference to NDAs 205836, 205827, 205838, please submit the following by COB June 19, 2015:

- 1) In response #1 in the safety information amendment (June 5, 2015), it was reported that multiple studies collected creatine phosphokinase and lactate dehydrogenase. Please provide pooled analyses for these laboratory tests (similar to those provided in the ISS for the other chemistry parameters).
- 2) In the ISS, it is stated that “all AEs related to overdose during clinical development of BRV were related to accidental or intentional (suicide attempts) overdoses with other drugs.” Subject N01379-028-00267 experienced an AE coded to “incorrect dose administered” with the verbatim term “nausea, hemoptysis after extra doses study drug taken.” Please provide a list of all subjects (along with BRV dose and AEs) who developed AEs related to overdose due to BRV for the data cut-off date for the 120-day Safety Update.
- 3) The narratives for some subjects (e.g.,) do not contain all of the AEs that occurred in the trial. For example, narratives for subjects N01125-576-2002, N01119-1362-0004, and N01199-1373-0002 do not list or describe the AE of thyroid neoplasm. Please explain.
- 4) Please provide a table (using the following table shell – a different table for Pool S4, Pool IV, Pool monotherapy, Pool Unverricht-Lundborg Disease, Pool Other, Pool Pediatric, Pool Phase 1 – using the data cut-off for the 120-day Safety Update) for all TEAEs in BRV-treated subjects in the SOC Neoplasms benign, malignant that includes hyperlinks to the narratives for these neoplasm-related TEAEs (please provide these narratives in the Appendix of the same document). Provide an additional summary table for only those subjects with malignant neoplasms with a study day of start of TEAE of ≥ 6 months (provide hyperlinks to the narratives) – stratified by pooled group. If the subject was diagnosed with a thyroid neoplasm (specifically a thyroid nodule), please specify whether a biopsy was performed for that subject and the pathology results.

Subject # (provide both core and LTFU numbers)	Age, Sex, Race	BRV Dose	Adverse event preferred term	Study day of start of AE (i.e., # of days after first BRV dose)	Medical history	Tobacco status

Please respond by June 19, 2015. Thank you.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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/s/

CATHLEEN B MICHALOSKI
06/12/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Monday, June 08, 2015 10:28 AM
To: Kristen.Piatak@ucb.com
Subject: Brivaracetam clinical/safety IR 205836, 7 & 8

Importance: High

Good Morning Kristen,
We have another clinical/safety request from the reviewer:

In reference to NDAs 205836, 205827, 205838, please submit the following by COB June 12, 2015:

- 1) Please provide an assessment of the effects on growth in pediatrics.
- 2) Provide the outcome for the 2 pregnancies from the ongoing LTFU studies (babies due in March 2015 and April 2015). Provide the outcome for the 1 additional report of a delivery (as of the cutoff date for the 120-day Safety Update).
- 3) Please confirm that there were no congenital malformations identified in any of the outcomes of “normal childbirths” or “healthy baby.”
- 4) There are 2 subjects in ISS Table 9-13 listed with the same subject number N01252-270-F410 (and N01125-649-2007) with outcome spontaneous abortion but with 2 different BRV daily doses at the time of pregnancy. Please identify the additional subject with the outcome of spontaneous abortion.
- 5) For all of the outcomes of spontaneous abortions, please report the obstetric history and past medical history of each subject.
- 6) For subject N01193-203-0229, please confirm that the fetal examination findings are still not available.

Thank you and as always any questions, do not hesitate to call.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
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CATHLEEN B MICHALOSKI
06/08/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Friday, June 05, 2015 12:04 PM
To: Kristen.Piatak@ucb.com
Subject: Brivaracetam clinical/safety IR 205836, 7 & 8

Importance: High

Good Afternoon Kristen:

We have the following information requests from our clinical/safety reviewer.

In reference to NDAs 205836, 205827, 205838, please submit the following by COB June 12, 2015:

- 1) The ISS tables 5.2.1.2.1 and 5.3.2.2.1 for Pool iv (along with the associated subgroup tables) do not include any TEAEs from studies N01256A, N01256B, and EP0007 (which are included in ISS Table 5.2.1.3.6 for Pool Phase 1 iv). Please explain. Please update all of the tables for Pool iv in the ISS (e.g., also ISS table 5.1.2.1).
- 2) In the ISS, it is reported that 1 subject discontinued due to the TEAE of gamma-glutamyltransferase increased in Pool iv (Table 5.6.2.1). However, after reviewing the CSRs for N01256A, N01256B, EP0007, and N01258, there is 1 BRV subject who discontinued due to the TEAE of anxiety in Study N01258. The subject numbers are also different between these 2 subjects. Please explain and provide updated ISS tables. Please also verify that all of the information in the ISS and 120-day Safety Update provide accurate pooled information for the pooled groups.
- 3) Using the 120-day Safety Update datasets, the analyses performed for Pool S1 result in different numbers than when using the ISS datasets (e.g., incidence of TEAEs for Pool S1, using the ISS algorithm for Table 5.2.1.1.1). Please explain. Please confirm that the 120-day Safety Update datasets contain updated information regarding the ongoing studies while containing the information in the original ISS datasets for all of the pooled groups (except for the clinical pharmacology studies).
- 4) Please provide a new ADSL dataset (data cut-off October 1, 2014) that includes all of the subjects in the entire safety database with one entry per subject (rather than splitting the demography file into ADSL, ADSLO, and ADSLP1).
- 5) Please provide tables for the incidence of PCST laboratory results (all hematology and chemistry parameters) for subjects with normal values at baseline for all pooled groups. Also provide tables for consecutive PCST laboratory results for ≥ 2 visits (for subjects with normal values at baseline) for all pooled groups.

Thank you, and questions do not hesitate to contact me.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
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CATHLEEN B MICHALOSKI
06/05/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, May 28, 2015 6:47 PM
To: Kristen.Piatak@ucb.com
Subject: Brivaracetam Information Request- safety /clinical

Importance: High

Good Evening Kristen,

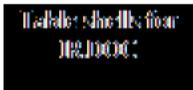
We have the following clinical information requests from our safety reviewer:

In reference to NDAs 205836, 205827, 205838, please submit the following by COB June 5, 2015:

- 1) Please list all of the studies that collected the following laboratory parameters: magnesium, creatine phosphokinase, and lactate dehydrogenase.
- 2) Please provide the possibly clinically significant treatment-emergent (PCST) criteria for the following laboratory values: chloride and phosphorus (inorganic). These values were not included in the ISAP Appendix 5.1.1.
- 3) Provide the following tables:
 - a. The 2 table shells included in the attached document.
 - b. An updated table for ISS Table 1.2.2 using the 120-day Safety Update data cut-off date.
 - c. An updated table for ISS Table 5-2 using the 120-day Safety Update data cut-off date. Additionally, include a row to delineate the number of subjects who took both solid oral dosage forms (tablet, capsule) and oral solution. The total # of subjects (n=3776) should equal the # subjects who took solid dosage form plus the # who took the oral solution plus the # who were give the iv injection (minus # subjects who took both solid and oral solution).
 - d. An updated table for 120-day Safety Update Table 1 that includes the following additional columns: total # of subject-years of BRV exposure, total # of subjects exposed to ≥ 6 months of BRV, and total # of subjects exposed to ≥ 12 months of BRV.
 - e. A table that includes the total subject-years of exposure for both the placebo and total BRV groups for all 6 of the Clinical Pharmacology Study Pools.

Again, please submit by June 5, 2015. Any question do not hesitate to contact me.

Thank you.



Cathleen Michaloski, BSN, MPH, RAC
Sr. Regulatory Project Manager

*Division of Neurology Products
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CATHLEEN B MICHALOSKI
05/28/2015



NDA 205836
NDA 205838

INFORMATION REQUEST

UCB, Inc.
Kristen Piatak, RAC, Associate Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brivaracetam Tablets 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg and Brivaracetam Oral Solution.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA 205836 and NDA 205838 by Friday, June 19, 2015.

LIST OF COMMENTS AND INFORMATION REQUESTS

We have received your response to NDA 205836 dated March 10, 2015, in which you proposed (b) (4) which is not acceptable per 21 CFR 211.165 (a) and (b). Amend the application to have the bioburden test as a stability test (b) (4) in the stability protocol (section P.8) (b) (4). Provide the method suitability report supporting the bioburden testing.

Your proposal to (b) (4) for NDAs 205836 and 205838 also results in (b) (4). Therefore, amend these applications (b) (4).

All batches of the injectable grade (NDA 205837) should be tested as proposed.”

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

{See appended electronic signature page}

Martha R. Heimann, Ph.D.
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MARTHA R HEIMANN
05/22/2015



NDA 205836
NDA 205837
NDA 205838

MID-CYCLE COMMUNICATION

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

Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs

Dear Ms. Piatak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for brivaracetam.

We also refer to the teleconference between representatives of your firm and the FDA on May 6, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH, RAC
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Teleconference Date: May 6, 2015, 3:00 pm – 3:30 pm
Application Number: NDA 205836 (oral tabs)
NDA 205837 (IV)
NDA 205838 (oral soln)
Product Name: brivaracetam (Briviact)
Indication: [REDACTED] (b) (4)
Applicant Name: UCB, Inc.
Meeting Chair: Norman Hershkowitz, M.D., Ph.D., Clinical Team Leader
Recorder: Cathleen Michaloski, BSN, MPH, Project Manager

FDA ATTENDEES

Norm Hershkowitz, M.D., Ph.D., Clinical Team Leader
Steve Dinsmore, D.O., Clinical reviewer
Mary Doi, M.D., M.S., Safety reviewer
Nahleen Lopez, PharmD, Regulatory Project Manager
Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager

APPLICANT ATTENDEES

Kristen Piatak, Associate Director, US Regulatory Affairs
John Whitesides, Ph.D., Senior Clinical Program Director
Jimmy Schiemann, M.D., Senior Medical Director
Deb Hogerman, Vice President, North America Regulatory Affairs
Laurence Leonardy, Director, Global Regulatory Affairs
Elena W. Cleary, Ph.D., Mission Lead, Epilepsy

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

NDA 205836
NDA 205837
NDA 205838
Mid-Cycle Communication

No significant issues have been identified to date.

During the teleconference the sponsor was informed of ongoing issues, none of which were considered to be significant at the present time. These include, the fact that a bioequivalence inspection consult was recently issued, that there were no significant chemistry issues at this time, and that the Division may issue an information request to clarify some of the unique patient identifiers in the controlled trial data. The sponsor was also informed that we received their response to our request for clarification of SUDEP cases, which are presently being reviewed. This, as well at the present time, is not considered to be a significant issue.

3.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

4.0 ADVISORY COMMITTEE MEETING

There are no plans for an Advisory Committee at this time.

5.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

We have tentatively scheduled our late cycle meeting for July 29, 2015, 10:00-11:00 am (EST). This meeting can be either a face to face meeting or a teleconference. We are also scheduled to review the pediatric proposals of the application on September 16, 2015. Finally, we plan to begin labeling negotiations and any post market requirements by September 20, 2015.

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/s/

CATHLEEN B MICHALOSKI
05/20/2015



NDA 205836

INFORMATION REQUEST

UCB, Inc.
Kristen Piatak, RAC, Associate Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brivaracetam Tablets 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA 205836 by Wednesday, 20 May 2015.

LIST OF COMMENTS AND INFORMATION REQUESTS

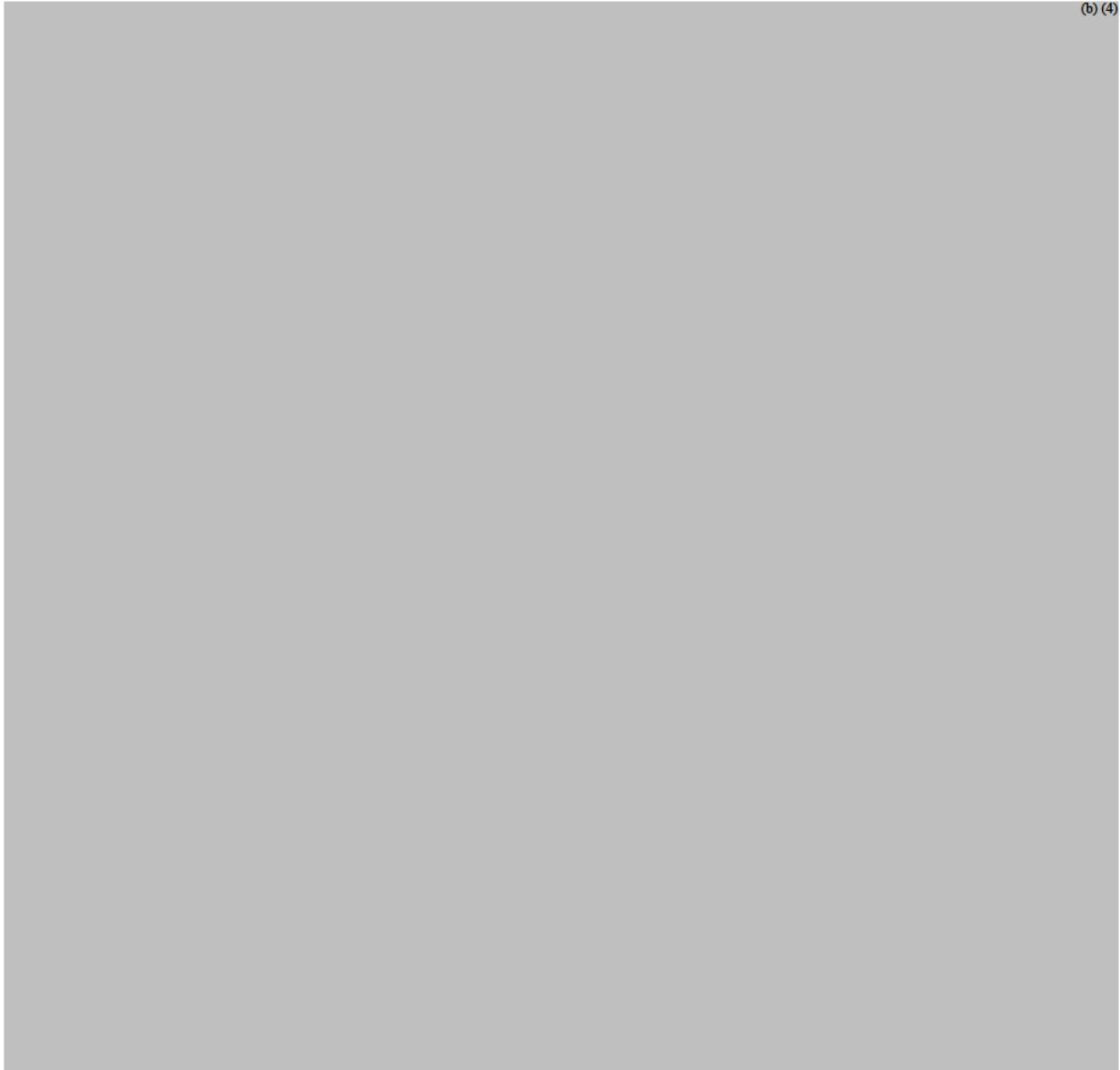
Biopharmaceutics:

1. Although the proposal to replace dissolution with disintegration as a release test and in the stability protocol seems reasonable [REDACTED] ^{(b) (4)} the correlation between disintegration and dissolution could not be verified. In addition, there are no data in the NDA to support a greater discriminating power of disintegration over dissolution. Provide the raw (individual vessel) data used to establish the correlation between dissolution and disintegration that is depicted in Figure 1-2 in section 3.2.P.5.6, and provide a comprehensive description of the quantitative relationship between the two test methods. Alternatively, provide data to demonstrate that disintegration is a more discriminating test than dissolution.
2. Provide the individual vessel disintegration data for the clinical and primary (as well as secondary) stability batches at release and during stability that support the proposed disintegration acceptance criterion of "NMT [REDACTED] ^{(b) (4)} min". Present the data graphically and in tabular format accompanied by a scientific rationale that supports the proposed acceptance criterion.

3. Justify the use of [REDACTED] ^{(b) (4)} as the medium for disintegration testing. Note that disintegration of Brivaracetam occurs [REDACTED] ^{(b) (4)}; the disintegration medium is not acceptable.

Process:

1. The proposed control strategy is not acceptable for the following reasons:



2. It is indicated in the Manufacturing Process Description that 'manufacturing equipment can be replaced by any equipment of similar performance'. Revise the statement to include that impact of replacement of equipment would be evaluated in concurrence with available guidances such as SUPAC guidance and Manufacturing Equipment Addendum.

Drug Product:

1. The following points of concern are associated with the [REDACTED] (b) (4)
[REDACTED]
 - a. The microbiological attributes of Brivaracetam tablets were analyzed as part of the pharmaceutical development (Module 3, Section 3.2.P.2). Results from multiple batches were provided. However, it is unclear how the drug product was packaged during testing. Confirm that microbial testing was performed with the drug product in both blister and bottle packaging configurations.
 - b. On page 155 of the stability data (Module 3, Section 3.2.P.8.3), you indicate that Brivaracetam 10 mg film-coated tablets met the specification for microbiological quality. However, raw data is not included. Provide the raw data.
 - c. [REDACTED] (b) (4)
2. [REDACTED] (b) (4)
3. [REDACTED] (b) (4)

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

{See appended electronic signature page}

Martha R. Heimann, Ph.D.
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

DAHLIA A WOODY
05/01/2015

MARTHA R HEIMANN
05/01/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, April 30, 2015 11:40 AM
To: Kristen.Piatak@ucb.com
Subject: FW: Information request from Medication Errors Staff - Briviact NDAs

Importance: High

Good Morning Kristen,
I received my message back so I am resending:

In response to your email of 4/29/15, please see reviewer comments below in RED. We also include this additional request:

We note there will be a (b) (4). Please send a description and picture of (b) (4) the commercial packaging of the oral solution.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
Bldg. 22, Room 4342
10903 New Hampshire Ave
Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov
301-796-1123*

From: Kristen.Piatak@ucb.com [<mailto:Kristen.Piatak@ucb.com>]
Sent: Wednesday, April 29, 2015 11:53 AM
To: Michaloski, Cathleen
Subject: RE: Information request from Medication Errors Staff - Briviact NDAs

Hi Cathy,
In regards to the Medication Errors Staff information request number 1, we wanted you to be aware of 2 items.

1) We noticed that we inadvertently did not include the hospital unit dose packages in the How Supplied section of the prescribing information but the associated proposed container labeling was provided in the original application. We will add the hospital unit dose to the PI now with the planned NDC numbers but wanted you to be aware of this difference from the previously submitted prescribing information. **We will need the revised prescribing information which includes the hospital unit dose packages in the How Supplied section.**

2) Regarding the 14-count blister packaging for the professional samples - in the original application we proposed (b) (4). After completing our packaging testing, we discovered this was not going to work as we planned. We would like to therefore, proceed with (b) (4). This would mean the (b) (4)

(b) (4). We would like to include this change, along with the NDC number, within the response. **Yes, we would need this revised label/labeling submitted for our review.**

We intend to include a response document with the submission, so the reviewers are aware of these 2 changes. Could you please advise if this approach is not acceptable? We are currently working to update the artwork so we can meet the May 4 deadline. **Acceptable**

Regarding request number 2: We will not be able to provide the samples with the labeling information on May 04. We are assessing how quickly we can provide these, but we are not currently in the production phase, and this could take many weeks.

We wanted to discuss a proposal that we could potentially have in about 2 weeks, if it would meet your needs. We would provide the printed cartons and approximate size sheets of (b) (4) but not the formed blisters. We will use the artwork we will submit in the response so the printed samples will include the NDC numbers. Once we confirm what is needed, we can complete our assessment and provide you a definite timeline. **Printed samples utilizing the revised artwork of non- formed blisters and printed cartons for the blister packs will be acceptable.**

We can still submit the unprinted samples on 04 May. Would this help with the review to do so? **See above comment, i.e., submit printed samples with revised artwork in approximately 2 weeks.**

The 50mg Sample Carton pdf included in the application contained 4 pages of pictures of a paper mock up. We wanted to ensure the reviewers were aware of this in case it helps continue the review. **Yes, we have these pictures which are helpful in continuing our review.**

We realize that follow up with DMEPA may be needed but we would still appreciate the opportunity to discuss with you. Kind regards,

From: Kristen.Piatak@ucb.com [<mailto:Kristen.Piatak@ucb.com>]
Sent: Wednesday, April 29, 2015 11:19 AM
To: Michaloski, Cathleen
Subject: RE: Information request from Medication Errors Staff - Briviact NDAs

Thank you Cathleen. We will not be able to meet the May 4th date for this part of the request. We would like to also discuss this point during our call at noon.
Kind regards,
Kristen

From: Michaloski, Cathleen [<mailto:Cathleen.Michaloski@fda.hhs.gov>]
Sent: Wednesday, April 29, 2015 8:37 AM
To: Piatak Kristen
Subject: FW: Information request from Medication Errors Staff - Briviact NDAs

Kristen,
To better understand the layout of information on the label, the reviewer would need the 14-count professional samples packaging to include all labeling information. Please let us know if you can meet the May 4th date. I will call you at noon.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
Bldg. 22, Room 4342
10903 New Hampshire Ave
Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov
301-796-1123*

From: Kristen.Piatak@ucb.com [<mailto:Kristen.Piatak@ucb.com>]
Sent: Tuesday, April 28, 2015 03:04 PM
To: Michaloski, Cathleen
Subject: RE: Information request from Medication Errors Staff - Briviact NDAs

Hi Cathleen,

We will submit the revised label and labeling reflecting the intended product NDC #s as requested.

For item 2, can you please provide further clarity on the request for the 3 samples of the 14-count professional samples packaging? We currently have unprinted, actual size packaging components that can be provided by close of business May 4. Is this acceptable to address your request?

Can you also please confirm, should the 3 samples be sent directly to your attention?

Kind regards,
Kristen

From: Michaloski, Cathleen [<mailto:Cathleen.Michaloski@fda.hhs.gov>]
Sent: Tuesday, April 28, 2015 10:04 AM
To: Piatak Kristen
Subject: Information request from Medication Errors Staff - Briviact NDAs
Importance: High

Dear Kristen,
Re: carton and container labeling:

1. The submitted proposed container labels and carton and prescribing information labeling denote "50474-XXX-XX" as a placeholder in the NDC # fields. Please submit revised label and labeling reflecting the intended product NDC #'s.
2. Please provide 3 samples of the 14-count blister packaging for the professional samples for the 25 mg, 50 mg and 100 mg strengths.

Please provide responses by COB, Monday, May 4, 2015.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration*

Bldg. 22, Room 4342
10903 New Hampshire Ave
Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov
301-796-1123

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/s/

CATHLEEN B MICHALOSKI
04/30/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, April 09, 2015 9:37 AM
To: Kristen.Piatak@ucb.com
Subject: Information request for Brivaracetam (NDA 205836)

Importance: High

Kristen,

We have an information request from our clinical pharmacology review team:

The subject IDs in the datasets for population PK/PKPD analyses (study CL0027 and study CL0028) and the subject IDs in the Data Analysis Data folders in Module 5.3.5.1 (SBJNBR for study N0114, N01193, N01252, and N01253; and USUBJID for N01358) are not consistent. Please align the ID information in the aforementioned population analysis datasets and individual study datasets to make them consistent.

Please provide response no later than COB Tuesday April 14th 2015.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

Bldg. 22, Room 4342

10903 New Hampshire Ave

Silver Spring, MD 20993

Cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI
04/09/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, March 19, 2015 3:09 PM
To: Kristen.Piatak@ucb.com
Subject: BRVIACT clinical safety information request

Importance: High

Good Afternoon Kristen,

We have a request from the safety team:

In reference to NDAs 205836, 205827, 205838, please submit the following by COB March 26, 2015:

- 1) For subject N01125-518-2003, the company causality of the death was considered “related” (per Table 6-27 of the ISS). However, the narrative includes information that all of the TEAEs were considered “unlikely related” to brivaracetam. Please clarify.
- 2) Submit all of the CIOMS forms for all of the deaths.
- 3) For subject N01199-1040-0002, it is reported in the ISS that the subject had a history of tobacco use. This history is not included in the narrative or the CRF. Please clarify.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

Sr. Regulatory Project Manager

Division of Neurology Products

ODE I/OND/CDER

Food and Drug Administration

Bldg. 22, Room 4342

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/s/

CATHLEEN B MICHALOSKI
03/31/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Friday, March 13, 2015 10:39 AM
To: Kristen.Piatak@ucb.com
Subject: Briviact clinical request N 205836,7, 8

Importance: High

Kristen,

We have the following information request from the clinical safety team:

Please submit the following by COB March 20, 2015:

Autopsy reports for all deaths in which autopsies were performed (please send the autopsy reports for the cases reporting definite/probable/possible SUDEP first).

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration
Bldg. 22, Room 4342
10903 New Hampshire Ave
Silver Spring, MD 20993
Cathleen.michaloski@fda.hhs.gov
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/s/

CATHLEEN B MICHALOSKI
03/31/2015

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Monday, March 30, 2015 3:38 PM
To: Kristen.Piatak@ucb.com
Subject: Brivacatam Information Request

Importance: High

Good Afternoon Kristen,
we have the following information request from the clinical safety reviewer.

In reference to NDAs 205836, 205827, 205838, please submit the following by COB April 10, 2015:

- 1) Confirm that all of the updated information contained in ISS for the 6 ongoing studies during the period between January 17, 2014 and June 25, 2014 is contained in the datasets and safety update summary submitted in the 120-day Safety Update.
- 2) In the ISS datasets, some TEAEs were uncoded or were coded to “unevaluable event.” However, most of the verbatim terms associated with these TEAEs contained information that should have been coded to MedDRA preferred terms (e.g., “depression with aggression”). Please explain. Please provide a listing of all TEAEs in the entire safety database that were uncoded or were coded to “unevaluable event” and the corresponding verbatim terms (and USUBJID) along with the reason that these were uncoded or coded to “unevaluable event”.
- 3) In reference to this patient (#07151) enrolled in N01372, please submit the autopsy report once available.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
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Bldg. 22, Room 4342
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Cathleen.michaloski@fda.hhs.gov
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/s/

CATHLEEN B MICHALOSKI
03/31/2015



NDA 205836

INFORMATION REQUEST

UCB, Inc.
Kristen Piatak, RAC, Associate Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brivaracetam Tablets 10, 25, 50, 75, 100mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA 205836 by Thursday, 26 March 2015.

LIST OF COMMENTS AND INFORMATION REQUESTS

Biopharmaceutics:

- i. Although the proposal to replace dissolution with disintegration as a release test and in the stability protocol seems reasonable [REDACTED] (b) (4) of Brivaracetam Tablets, the correlation between disintegration and dissolution could not be verified. In addition, there are no data in the NDA to support a greater discriminating power of disintegration over dissolution. Provide the raw (individual vessel) data used to establish the correlation between dissolution and disintegration that is depicted in Figure 1-2 in section 3.2.P.5.6, and provide a comprehensive description of the quantitative relationship between the two test methods. Alternatively, provide data to demonstrate that disintegration is a more discriminating test than dissolution.
- ii. Provide the individual vessel disintegration data for the clinical and primary (as well as secondary) stability batches at release and during stability that support the proposed disintegration acceptance criterion of "NMT [REDACTED] (b) (4) min". Present the data graphically and in tabular format accompanied by a scientific rationale that supports the proposed acceptance criterion.

iii. Justify the use of [REDACTED]^{(b) (4)} as the medium for disintegration testing. Note that disintegration of Brivaracetam occurs [REDACTED]^{(b) (4)}; the disintegration medium is not acceptable.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

{See appended electronic signature page}

Martha Heimann, PhD
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

DAHLIA A WOODY
03/18/2015

MARTHA R HEIMANN
03/18/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205836
NDA 205837
NDA 205838

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

UCB Inc.
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

ATTENTION: Kristen Piatak, RAC
Associate Director, Regulatory Affairs

Dear Ms. Piatak:

Please refer to:

- Your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act dated November 22, 2014, and received, November 22, 2014, for Brivaracetam Tablets, 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg.
- Your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, dated and received November 20, 2014, for Brivaracetam Injection, 10 mg/mL
- Your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, dated and received November 20, 2014, for Brivaracetam Oral Solution, 10 mg/mL

We also refer to:

- Your correspondence, dated and received December 3, 2014, requesting review of your proposed proprietary name, Briviact, and your subsequent amendment, dated and received, December 9, 2014
- Your correspondence, dated and received December 9, 2014, requesting review of your proposed proprietary name, Briviact
- Your correspondence, dated and received December 3, 2014, requesting review of your proposed proprietary name, and your subsequent amendment, dated and received, December 9, 2014

We have completed our review of the proposed proprietary name, Briviact and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 3, and 9, 2014, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted. If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Cathleen Michaloski, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/27/2015



NDA 205836
NDA 205837
NDA 205838

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

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

Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs

Dear Ms. Piatak:

Please refer to your New Drug Applications (NDA) dated and received as per below table under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for BRIVIACT (brivaracetam).

PRODUCT	NDA #	Letter Date	Date Submitted	Date Received
Brivaracetam tablets, 10, 25, 50 and 100 mg	205836	November 19, 2014	November 22, 2014	November 24, 2014
Brivaracetam Solution for injection 10mg/mL	205837	November 19, 2014	November 20, 2014	November 20, 2014
Brivaracetam Oral Solution 10mg/mL	205838	November 19, 2014	November 20, 2014	November 20, 2014

We also refer to your amendments dated December 3, 9, and 22, 2014, and January 7, and 12, 2015.

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**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>)

The submission/letter date for each NDA is noted as November 19, 2014. However, the receipt dates are November 20, 2014 (IV and oral solution) and November 24, 2014 (tablets). Due to

the discrepancy resulting from the delayed receipt date of the tablet NDA, we have determined the goal date based on the earlier receipt date.

Therefore, the user fee goal date is November 20, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 20, 2015. In addition, the planned date for our internal mid-cycle review meeting is April 27, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Requested Product Quality Information

- 1) Your applications lack sufficient detail regarding development of the manufacturing processes, and the proposed commercial processes. Therefore, provide the following information to each NDA:
 - a) Submit the following information to Section 3.2.P.2:
 - i) Data to support the selection of controlled process parameters and the proposed ranges. Indicate what is the potential impact (i.e., criticality) of the controlled process parameters on the finished product Critical Quality Attributes.
 - ii) Data to support selection and limits of proposed in-process controls. Please note that the Table 1-1 in section 3.2.P.3.3 is confusing as it includes both process parameters and in-process controls without distinguishing between them. Revise Table 1-1 to delineate what are the process parameters and what are in-process controls.
 - iii) Comprehensive discussion of the approach to scale up the process, including comparison of ranges of process parameters and equipment types at various scales.
 - b) In compliance with 21 CFR 314.50 (d)(1)(ii)(c), a complete description of the commercial scale manufacturing process is required. You can either revise the manufacturing process description in section 3.2.P.3.3 to include set points/ranges for the process parameters, batch size and equipment type and size for all unit operations of the

drug product manufacturing process or submit proposed commercial scale Master Batch Records to Section 3.2.R.

2) For NDA 205836, Brivaracetam Tablets:

a) The specification for Brivaracetam tablets on release includes only an (b) (4) for identification. As the drug substance is an enantiomer, please include an additional test confirming the drug substance's stereochemistry, as per ICH Q6A and the guidance, "Development of New Stereoisomeric Drugs".

b) You propose (b) (4). This proposal may be acceptable provided adequate (b) (4) controls are established and documented. More information on your process is needed. Address the following points:

- i) (b) (4)
- ii) (b) (4)
- iii) (b) (4)

In addition to these points, you should minimally perform (b) (4) Provide an updated stability schedule to reflect this testing.

3) For NDA 205837, Brivaracetam Injection:

- a) Provide a list of equipment used in the manufacturing process.
- b) Provide data supported justification (the acceptance criteria and test results) for the proposed (b) (4).
- c) The method suitability testing supporting the sterility and the endotoxin testing of the final product could not be located in the submission. Provide either the location in the submission or provide the reports.

4) For NDA 205838, Brivaracetam Oral Solution:

- a) Provide a list of equipment used in the manufacturing process.
- b) Submit detailed description and controls for the (b) (4) steps.
- c) (b) (4) is listed as both a release and a stability specification. However, (b) (4) is monitored during release and stability testing. Please clarify if (b) (4) is monitored during release and stability studies.

- d) The method suitability testing supporting the final product for microbial limits testing per USP <61> and <62> could not be located in the submission. Provide either the location in the submission or provide the reports.
- e) Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism [REDACTED] ^{(b) (4)}. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided.
- f) Oral solution batches BX1010713, BX1010714, and BX1010140 are identified in section 3.2.P.5.4 as process validation batches. However, in section 3.2.P.8.1 the batch numbers given for process validation batches are 113946, 113928, and 115984.
 - i) Clarify the relationship between the batches listed in section 3.2.P.5.4 and those listed in section 3.2.P.8.1.
 - ii) Clarify whether these batches were manufactured using the proposed commercial process as delineated in section 3.2.P.3.3.
- g) Submit a representative executed batch record for a batch manufactured using the commercial manufacturing process delineated in 3.2.P.3.3.

Requested Clinical Datasets Information

- 1) Study 1252
 - a. In the clinical study report (CSR), you presented summary data (Table 8:1) and efficacy results (Table 8:2) with 100 subjects in the brivacetam 100 mg group. We only found 99 subjects in the brivacetam 100 mg group for the treatment period in dataset effszp. One subject (122/D160) does not have seizure data during the treatment period. Please clarify if you have carried over baseline seizure frequency or used other imputation in your analyses.
 - b. It is not clear which stratification variable is used for the efficacy analysis. The labels strat1 and strcombf are not clear. Please clarify.
- 2) Study 1253 (dataset effszp)
 - a. In the clinical study report (CSR), you presented summary data (Table 8:1) and efficacy results (Table 8:2) with 392 subjects in efficacy population. There are 99 subjects in the brivacetam 20 mg group. We found 100 subjects in the brivacetam 20 mg group with no missing seizure data for both the baseline and treatment

period. Although you have listed one subject (no subject ID was provided) in the brivacetam 20 mg group that was excluded from the mITT population, we could not find the explanation for the exclusion. In the brivacetam 5 mg group, your analysis included 96 subjects for both baseline and treatment period. We found 98 ITT subjects in the group with 3 subjects missing the treatment data. Therefore, we only found 95 subjects with seizure data for both baseline and the treatment period. In the placebo group, we found 99 subjects in the ITT population, all of which have baseline data with one missing the treatment data, whereas you listed 98 subjects in the ITT population with 96 of them included in the analysis. Please explain these discrepancies.

- b. It is not clear which stratification variable is for the efficacy analysis. The labels strat1 and strcombf are not clear. Please clarify.

3) Study 1358

Please provide information with regard to pooling of countries. Please provide the pre-specified plan if there is one, or otherwise provide the list of pooled countries with variables used in your analysis. Please also provide information with regard to stratification variables in the dataset that is used in your analysis.

Requested Clinical Pharmacology Information

Please direct us to the location of the following documents within the respective NDA submission:

- 1) Report for UCB Study Number TA0668 (validation report referenced in the clinical study report for Study 01171, NDA 205836). If this validation report is not present in the current submission, please submit the report.
- 2) Report(s) of calibration and performance for bioanalytical assay utilized in Study EP0007 as well as Study N01258 (NDA 205837).

If any of the aforementioned documents are not present in the current submissions, please submit them.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

We did not identify any significant format issues with the proposed labeling.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Neurology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies (neonate age group birth to <1 month of age) for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies (age range of 1 month to < 16 years) for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Cathy Michaloski, Sr. Regulatory Project Manager, by email at Cathleen.michaloski@fda.hhs.gov or by phone at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Eric P. Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ERIC P BASTINGS
02/02/2015



NDA 205836
NDA 205837
NDA 205838

NDA ACKNOWLEDGMENT

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

Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs

Dear Ms. Piatak:

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

Name of Drug Product: BRIVIACT (brivaracetam); 10, 25, 50, 75, and 100 mg oral tablets; injection (10 mg/mL); and oral solution (10 mg/mL)

Date of Application: November 19, 2014

Date of Receipt: November 20, 2014

Our Reference Number: NDA 205836 (oral tablets)
NDA 205837 (injection 10 mg/mL)
NDA 205838 (oral solution 10 mg/mL)

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 19, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

NDA 205836
NDA 205837
NDA 205838
Page 2

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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact me by email at Cathleen.michaloski@fda.hhs.gov, or by phone at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH, RAC
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

CATHLEEN B MICHALOSKI
12/01/2014



INDs 070205,103908, 110606

ADVICE/INFORMATION REQUEST

UCB, Inc
Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brivaracetam.

We also refer to your amendment dated August 22, 2014, containing your Resubmission 2-Agreed initial pediatric study plan (iPSP).

We acknowledge your plan to study brivaracetam in pediatric patients (\geq 1 month to (b) (4) years of age) as adjunctive treatment for partial-onset seizures. We have completed our review of the submission, and we confirm our agreement to your Agreed iPSP. We have no further comments on your PSP. A clean copy of the Agreed iPSP is attached for your reference.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, please contact Heather Bullock, Project Manager, via e-mail at heather.bullock@fda.hhs.gov or via telephone at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

41 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ERIC P BASTINGS
09/30/2014

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

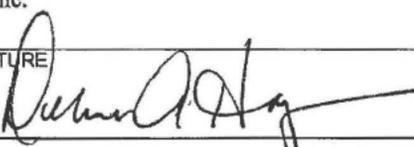
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the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

Please mark the applicable checkbox.

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

Clinical Investigators	See Attached Table	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Deb Hogerman	TITLE Vice President, North America Regulatory Affairs
FIRM/ORGANIZATION UCB Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) Sep 25 2014

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850



IND 070205
IND (b) (4)
IND 103908
IND 110606

MEETING MINUTES

UCB, Inc.
Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brivaracetam.

We also refer to the meeting between representatives of your firm and the FDA on July, 29, 2014. The purpose of the meeting was to discuss the NDA submission strategy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Heather Bullock, Regulatory Project Manager, via email at heather.bullock@fda.hhs.gov or via telephone at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: July 29, 2014 at 2:00 pm Eastern Standard Time

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: INDs: 070205; (b) (4) 103908; 110606

Product Name: brivaracetam
Indication: adjunctive therapy in the treatment of partial onset seizures in patients 16 years and older with epilepsy
Sponsor/Applicant Name: UCB, Inc.

FDA ATTENDEES

Ellis Unger, MD, Director, Office of Drug Evaluation I
Bob Temple, MD, Deputy Director, Office of Drug Evaluation I
Billy Dunn, MD, Acting Director, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Director, DNP
Norm Hershkowitz, MD, Clinical Team Leader/Reviewer, DNP
Kevin Krudys, PhD, Pharmacometrics Team Leader (Acting), Office of Clinical Pharmacology (OCP)
Mike Bewernitz, PhD, Clinical Pharmacology Reviewer, OCP
Chad Reissig, PhD, Pharmacologist, Controlled Substance Staff
Shastri Bhamidipati, PhD, CMC Reviewer, Office of New Drug Quality Assessment
Denise Miller, BS, Quality Micro Reviewer, Office of Pharmaceutical Science
Kun Jin, PhD, Biometrics Team Leader, Division of Biometrics I
Julia Luan, PhD, Statistical Reviewer, Division of Biometrics I
Jared Lantzy, Operations Research Analyst, Office of Business Informatics
Christopher Toscano, PhD., Nonclinical Reviewer, DNP
Felecia Duffy, Risk Management Analyst, Division of Risk Management
Christina Kirby, PharmD, User Fee Staff
Tiffany Kong, Pharmacy Student Intern, DNP
Susan Daugherty, Regulatory Project Manager, DNP
Heather Bullock, Regulatory Project Manager, DNP

EASTERN RESEARCH GROUP ATTENDEE

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Kristen Piatak, Associate Director, US Regulatory Affairs
Deb Hogerman, Vice President, North America Regulatory Affairs
Laurence Leonardy, Director, Global Regulatory Affairs
Jimmy Schiemann, MD, Senior Medical Director
Armel Stockis, PhD, Senior Director, Clinical Pharmacology CNS
John Whitesides, PhD, Senior Clinical Program Director
Martin E. Johnson, MS, Principal Biostatistician
Judith Domville, Associate Director, Global CMC Regulatory Affairs
Elena W. Cleary, PhD, Mission Lead, Epilepsy
Michael Malone, VP PST Leader Brivaracetam
Belinda McDonough, MB BCh BAO, Director Safety Lead (CNS), Drug Safety
Phyllis Smetana, Project Statistical Programmer

1.0 BACKGROUND

IND 070205 for brivaracetam solid oral dosage formulations was submitted on July 12, 2004, for the treatment of epilepsy.

Brivaracetam is a new chemical entity that is structurally related to piracetam and levetiracetam.

(b) (4)

(b) (4)

On December 11, 2006, an End-of-Phase 2 meeting was held to discuss the Phase 3 development of brivaracetam as adjunctive therapy in the treatment of partial onset seizures (b) (4) in adults with epilepsy.

(b) (4)

(b) (4)

IND 103908 for brivaracetam intravenous formulation was submitted on October 30, 2008, (b) (4)

(b) (4)

On January 19, 2010, a Type C meeting was held to discuss the results of the brivaracetam Phase 3 studies for adjunctive therapy in partial onset seizures and an additional proposed Phase 3 supportive study. In the preliminary comments, the Division did not concur (b) (4)

IND 070205

IND (b) (4)

IND 103908

IND 110606

Page 2

(b) (4). The Division stated that the dose/response for such an effect did not appear to be fully explored. For example, the Phase 3 study N01252 was not a positive study based on the pre-specified primary efficacy analysis, with the 50 mg/day dose not reaching significance, but with the 100 mg/day dose nominally significant. Nonetheless, the dose of 50 mg/day was statistically significant in the other Phase 3 study, N01253, which met the pre-specified primary efficacy analysis, and was a positive study. The 50 mg/day dose failed in one of two Phase 2 studies as well, where the higher dose of 150 mg/day also failed. During the meeting, the proposed study was discussed. (b) (4)

The Division stated that UCB had not adequately looked at dose-response and strongly suggested that a higher dose be studied. In addition, the Division recommended that the study include three arms (50 mg, 100 mg, and 200 mg). (b) (4)

The Division stated that the proposal may be adequate. In the completed Phase 3 trial, patients on levetiracetam fared worse than patients not on levetiracetam. Therefore, the Division recommended that the trial not exclude patients on levetiracetam.

On September 14, 2010, a Special Protocol Assessment (SPA) Agreement letter was sent for IND 070205 protocol "N01358: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Evaluate the Efficacy and Safety of Brivaracetam in Subjects (≥ 16 to 80 years old) with Partial Onset Seizures."

IND 110606 for brivaracetam oral solution was submitted on November 19, 2010, for (b) (4)

(b) (4)

On March 8, 2012, a SPA Agreement letter was sent for an IND 070205 stability protocol.

(b) (4)

On December 26, 2012, the Division responded to a submission by UCB, referred to as an integrated statistical analysis plan (ISAP). Many of the questions covered the same topics as in this pre-NDA meeting request. For example, information was requested on pools to be provided in an ISS, subgroup safety analysis, required safety database exposures, required safety narratives, safety dataset format, etc.

On December 13, 2013, UCB submitted an initial pediatric study plan (iPSP) for INDs 070205, 103908, and 110606. On March 20, 2014, the Division responded with iPSP comments and recommendations in an advice letter. UCB subsequently submitted iPSP clarification questions on April 17, 2014. The Division answered those questions on May 28, 2014. UCB submitted an Agreed iPSP on June 13, 2014, and the Division responded on July 11, 2014, stating that they remain without agreement to their “Agreed iPSP.”

On March 12, 2014, UCB requested a Type B Pre-NDA meeting. UCB intends to file three NDAs to support a film-coated tablet, a solution for injection, and an oral solution of brivaracetam for adjunctive therapy in the treatment of partial onset seizures in patients 16 years and older with epilepsy. UCB would like to obtain concurrence that the NDAs, as planned, will provide adequate information to allow for a substantive review by the agency.

The purpose of this meeting is to discuss the NDA submission strategy.

2. DISCUSSION

Question 1: Does the Division concur that the stability data as described will be adequate to support filing and review of each NDA (tablet, oral solution, and solution for injection)?

We agree that proposed submission of stability data is, on face, adequate for filing and review of each NDA (brivaracetam tablets, oral solution and injection formulations).

Please be reminded that information for brivaracetam tablets packaged in bottle and blister configurations should include permeability and stability data for the two configurations that will be evaluated independently.

We have following additional comments about the three formulations:

Tablet Formulation: We recommend that the final drug product be tested for microbial quality, both at release and in the stability program. If, after approval of the NDA, you wish to exclude microbial quality testing for the final drug product, we recommend that a supplement that includes a justification for the removal of the microbial testing for product release be submitted. The justification should include the microbial contamination controls in place in the manufacturing process and historical data from the testing. Microbial quality testing should remain in the stability program.

Oral Solution: (b) (4)

(b) (4). The recommended approach would be to conduct a development study in which the various concentrations of (b) (4) are tested (b) (4). The concentrations selected to test should bracket the acceptable concentrations (b) (4) over the proposed shelf life of the product.

Intravenous Solution: The proposed specification for brivaracetam injection should include testing for osmolality, assuring its suitability for parenteral administration. The adequacy of the endotoxin specification will be a review issue in the NDA. The endotoxin limit should be based on the maximum intravenous dose and a (b) (4) EU/kg threshold.

Meeting Discussion:

CMC: (b) (4)
(b) (4). UCB agreed to provide all available data in the NDA and include osmolality testing in the drug product specification.

Micro: For the oral formulation, UCB stated (b) (4) and (b) (4) and agreed to include these studies in the NDA.

Question 2: Does the Division concur that the data to be included in the applications are adequate to support filing and review for the three NDAs?

Proposed eCTD format and description of line items in Modules 2 and 3 appear, on face, to be adequate for filing and review of the three NDAs.

We recommend that you provide in each application the full corporate names of the facilities in addition to the mailing address and the physical addresses of the respective sites. Include the FEI number and the specific responsibilities for each site. Also include the names and titles of the onsite contact persons along with their telephone numbers, fax numbers and email addresses. Provide a brief description of the operation being conducted at the facility including the type of testing and DMF number (if applicable). It is expected that each facility named in the application be inspection ready at the time the application is submitted.

Meeting Discussion: There was no discussion.

Question 3: Are the nonclinical studies proposed for inclusion in the NDA, and outlined in this briefing package, adequate to support filing and review of the applications?

The proposed nonclinical studies appear sufficient to support filing of the applications. However, the adequacy of the studies will be a matter of review.

Meeting Discussion: There was no discussion.

Question 4: Are the clinical studies proposed for inclusion in the NDAs, and outlined in this briefing package, adequate to support filing and review of the applications?

From a clinical perspective, the clinical studies proposed for inclusion in the NDAs for the tablet and oral solution appear, on face, adequate for filing. There is insufficient information to make this determination regarding the safety analysis for the intravenous formulation. The safety information must allow a determination as to whether there is a safety signal unique to intravenous administration. Safety data must be reported in epochs that include the pre-infusion baseline period, the infusion period, the period immediately post-infusion, and periods between infusions for multiple dosing. These data should include vital signs, EKGs, and adverse event reporting. Vital signs should include central analysis, shift tables, and outlier analyses.

We also refer you to our December 26, 2012, response to your ISAP.

Meeting Discussion:

UCB noted that there was no standardized analysis of time points between studies for the evaluation of vital signs, EKGs, and AEs; i.e., all studies did not utilize the same data collection time point in relation to the dosing. The Division noted that this may be acceptable, but is ultimately a review issue. The Division noted that analyses during infusion would be required, at approximately T_{max} , as well as at least during the following one hour after infusion (**Post-meeting Note:** although one hour was noted at the meeting, any values beyond that time that were collected should be provided and analyzed in discrete epochs). In the case of a bolus, where evaluations during infusion may be difficult, evaluations at the approximate T_{max} should be provided. Values should be compared to pre-dosing baselines. An outlier and central (median and mean) analysis should be performed. Examples of outliers for vital signs were presented by UCB. The Division noted that these were acceptable. It was agreed that shift tables need not be constructed. The Division noted that analyses of vital signs and EKG in intravenous studies were very important and UCB should provide a well-integrated and well-analyzed discussion of any potential signal.

Question 5: Does the Division concur that the integrated safety database is sufficient to support filing and review of the applications?

On face, yes, except for the intravenous formulation (see our answer to Question 4).

Meeting Discussion: UCB noted that there are 175 to 177 patients in the intravenous database. The Division noted that on face this seems adequate, but it is ultimately an issue of review.

Question 6: Does the Division concur that the analyses described in the ISAP are adequate to support filing and review of the NDAs?

Yes.

Meeting Discussion: There was no discussion.

Question 7: Does the Division agree with UCB's proposal for presenting data on subjects with falls and subjects with injuries, including the plan for evaluating concurrence with seizures?

Yes.

Meeting Discussion: There was no discussion.

Question 8: Does the Division concur with:

- a. the exclusion of N01254 from the 3 proposed pooled pharmacometric analyses?

Yes, the exclusion of N01254 is acceptable.

Meeting Discussion: There was no discussion.

b. the non-exclusion of Phase 2 N01193 and N01114 from the pooled PK and PK/PD data sets and testing development phase (2/3) as an influential covariate in the model?

Yes, it is acceptable.

Meeting Discussion: There was no discussion.

c. the daily seizure count modeling approach outlined in the CL0027 exposure-response analysis plan?

Yes. In addition to the modeling approach using daily seizure frequency counts, we would like you to conduct an exposure-response analysis using the primary endpoint (log-transformed partial onset seizure frequency per 28 days).

We also recommend that you explore the relationship between exposure and safety for pertinent adverse events.

Additional Comment Regarding Datasets:

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Meeting Discussion:

UCB agreed to conduct an exposure-response analysis using the primary endpoint (log-transformed partial onset seizure frequency per 28 days) and to submit that analysis with the original application. UCB stated that it had not originally planned to explore the relationship between exposure and adverse events and noted that the rates of adverse events in patients treated with brivaracetam were low. UCB and the Division discussed which adverse events should be included in the exposure-response analyses. The Division advised UCB to consider selecting adverse events that will be listed in the highlights section of the label, or adverse events that occur more frequently in the treatment arm compared to placebo and

appear to be dose-related. UCB agreed to perform the analyses and will attempt to include them in the original application. If additional time is needed, the Division agreed that the exposure-response analysis for safety may be submitted within 30 calendar days after the submission of the original application.

Question 9: Does the Agency agree with the proposed methods for evaluating clinical trial data related to abuse and dependence potential, including potential abuse-related AEs, post-drug discontinuation AEs, diversion, and overdose?

- i. You must evaluate all AEs related to abuse potential, in addition to treatment-emergent AEs. See the draft guidance (below) for details on the AE analysis. We have included a list of abuse-related AEs in the attachment below (see Appendix 1).
- ii. Adverse event data related to abuse should be characterized and presented by gender, age (pediatric, non-pediatric, elderly, non-elderly, etc.), population (healthy volunteers, recreational drug users from the human abuse potential study, and patients), treatment, dose, time of onset, duration of AE, severity, and outcome. We suggest that you present the data in tabular format, for example:

Study number/Site number	Subject identifier (Sex/Age)	AE (preferred term/Verbatim term)	Treatment dose/exposure	Onset relative to dosing (h:m)	Duration (h:m)	Severity	Related?	Outcome	Site/Investigator comments (if any)

Notes:

- iii. Overall, we agree with your method for evaluating abuse-related AEs from clinical trials in the abuse potential assessment, although we want to see the reported AEs by population (see above). CSS cannot comment on your pooling strategy until full study reports are available for all of the completed clinical studies.
- iv. You should be prepared to provide case report forms and narratives for each of the abuse-related AEs observed.
- v. AE's following drug discontinuation should be presented separately. Details of the discontinuation process should be included and narratives should be provided. Information on concomitant medications should be provided as well as duration of treatment, onset of AE after discontinuation, etc. Again, refer to the table above for the type of information that should be collected.

- vi. An AE analysis may not be suitable to assess the ability of brivaracetam to produce physical dependence or a withdrawal syndrome upon abrupt discontinuation. You may need to perform a prospective clinical study of physical dependence and withdrawal.
- vii. CSS is available to review detailed protocols regarding your withdrawal and dependence liability assessment strategy.
- viii. A full review of the human abuse potential study (HAPS) has not been performed. However, a cursory review of the HAPS reveals that brivaracetam produces high levels of “drug liking” in recreational sedative users. These data suggest that brivaracetam is reinforcing, and as such, will be considered for scheduling under the Controlled Substances Act.
- ix. For additional information on the abuse potential assessment of drugs, see the draft guidance for industry “Guidance for Industry Assessment of Abuse Potential of Drugs” available online at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

Meeting Discussion: UCB said it would collect AEs using AE lists published by Sun and Love. CSS opined that the alternative AE list provided in the meeting comments is preferable to the list suggested by Sun and Love. CSS explained that the AE list suggested by Sun and Love may be overly inclusive and difficult to interpret, hence the recommendation to focus on the CSS-provided AE list in the appendix.

UCB agreed to provide AEs in a tabular format similar to the table CSS provided. CSS advised UCB that providing AEs in a format amenable to regrouping or rearrangement for additional analyses would be ideal. UCB agreed to provide CRFs for abuse related AEs.

UCB asked whether an *a priori* physical dependence study could be completed post-marketing. CSS deferred to the Division on the acceptability of performing the dependence study post-approval.

Post-Meeting Note:

CSS: UCB provided an additional description of the AE pooling strategy. On face, the strategy appears appropriate; however, without an in-depth review and analysis of the entirety of the clinical development program, the appropriateness of the pooling strategy will be a review issue when the NDA is submitted. For example, a gender analysis may

(or may not) be appropriate. UCB can examine reviews of previously approved products (e.g., suvorexant, lorcaserin, or perampanel) to see additional examples of CSS reviews.

Clinical: This is acceptable. The approval of a drug product is not dependent upon its scheduling. However, we remind you that you cannot market brivaracetam until DEA finalizes scheduling under the Controlled Substances Act (if required). If the dependence study delays scheduling, marketing of the drug may be delayed.

Question 10: Does the Division concur with:

- a. the proposed table of contents for the tablet application?**
- b. the proposed table of contents for the solution for iv injection application?**
- c. the proposed table of contents for the oral solution application?**

From a technical standpoint (not content related), the proposed format for the planned NDAs are acceptable. However, we have these additional comments:

- Study Reports should reside in m5 (not m1.3.1.4), under the respective Study Tagging File (STF) and file tagged as “study-report-body.”
- The list of investigators (single pdf file with bookmarks, table of contents and hyperlinks) should reside in m5 (not m1.3.4.) under the specific study’s STF and file should be tagged as “list-description-investigator-site.”
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be hyperlinked to the referenced studies in m5.
- Providing Table of Contents in m3.1 is not necessary in the eCTD structure.
- Study Tagging Files are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References, and m5.3.6, if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study’s STF, including case report forms (CRFs).

Case report forms need to be referenced under the appropriate STF to which they belong, organized by site as per the specifications and tagged

as “case report form.” Please refer to the eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

- Your options for cross-referencing information submitted to another application would be to either place a cross-reference document under module m1.4.4 (cross reference to other applications), or use cross-application links.
 - To use the first option (placing a cross-reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non-eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document, along with a hypertext link to the location of the information, when possible.
 - To use the second option (cross-application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. NDA, NDA). Also, when cross-application links are used, it is strongly recommended that a cross-reference document be placed in m1.4.4, in case any of the links do not work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word “cross-reference” and application number (e.g., Cross Ref to NDA123456). The cross-reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

Prior to using cross-application linking in an application, it is recommended that the sponsor submit an "eCTD cross application links" sample, to ensure successful use of cross-application links.

To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team -

esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at: - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionsRequirements/ElectronicSubmissions/ucm174459.htm>

Meeting Discussion: UCB stated that it might have issues with compiling the specific requested data into a single document as the eCTD specifications reference a 100 MB limit for file size. The Office of Business Informatics clarified that the 100 MB limit is outdated and the current file size limit is 400 MB for PDF documents.

Question 11: (b) (4)

(b) (4) For purposes of assessing user fees, original applications will be assessed a full user fee if clinical data (for safety or effectiveness) are required for approval.

NDA 205836 (oral tablet) requires clinical data, and NDA 205837 (solution for IV injection) may require clinical data for user fee purposes. NDA 205838 (oral solution) would probably not require clinical data for user fee purposes. Therefore, it appears to be 2 and ½ fees would be required for the three NDA submissions.

Please note that this user fee recommendation is based on current information, and the decision may change once the applications are submitted in their entirety.

Meeting Discussion: There was no discussion.

Question 12: Does the Division concur that N01252, N01253, and N01358 are the covered studies?

Yes.

Meeting Discussion: There was no discussion.

Question 13: If the answer to Question 12 is yes, does the Division then concur:

(b) (4)

(b) (4) Financial disclosures from the referenced studies will support the oral tablet. You should also provide financial disclosures for PK studies that support the bioequivalence for the oral solution and intravenous formulation, as well as disclosures for investigators participating in tolerability/safety studies for the intravenous formulation.

Meeting Discussion: There was no discussion.

b. that providing the Transfer of Obligation information previously submitted for the IND studies N01253 and N01358 and similar information for N01252 is adequate to support filing and review of the NDAs?

Resubmitting the transfer of obligation documents to the NDA is reasonable. For the foreign clinical study, referring to the clinical study report and not creating a new transfer of obligations document for N01252 is sufficient as long as you indicate the location of the required information by providing cross-reference (and/or hyperlinks) to relevant sections of the application.

Meeting Discussion: There was no discussion.

c. (b) (4)

(b) (4) As provided in your email response to our clarification request dated July 22, 2014, we understand that 37 of the 52 clinical studies did not include US sites and were not conducted under an IND. Although you note that the results/reports for these studies have been previously submitted to the IND, these studies account for a large number of patients, the “supporting data” that should be included in the NDA.

Meeting Discussion: UCB stated that it will incorporate all safety data from these studies into the application and the ISS. The Division concurred with this approach. UCB noted the missing information includes mainly CMC data in non-pivotal studies.

The Division asked UCB whether information for the drug substance and drug product batches used in the non-IND pivotal studies will be included and identified with traceability to Module 3 (Quality).

Following discussions on this point, the Quality Reviewer stated that this information should be included as part of the Pharmaceutical Development Report and also referred to the preliminary response for Question 14. UCB agreed to include complete information for drug substance and drug product batches used in the non-IND pivotal studies in the Pharmaceutical Development Report (Module 3 Section P.2.2) of the NDA for the tablet formulation, detailing the bridging with appropriate hyperlinking per the preliminary response provided for Question 14.

Question 14: Does the Division concur that the locations of the biowaiver request information are acceptable?

Yes, we concur. In addition, please provide in your NDA a diagram illustrating the bridging between the different formulations used in development (from initial to commercial). Please include the study number of the PK and clinical studies that used those formulations, as well as the study number for each in vitro dissolution study supporting the bridging between formulations. Include in the diagram the necessary hyperlinks as appropriate.

Meeting Discussion: There was no discussion.

Question 15: Does the Division concur with the proposed report formats for the ongoing studies?

Yes. In addition, the safety data from ongoing open label studies should be included in the ISS.

Meeting Discussion: There was no discussion.

Question 16: Does the Division concur that providing a list of all clinical sites in studies N01252, N01253, and N01358 will be adequate to support filing and review of the NDAs?

Yes.

Meeting Discussion: There was no discussion.

Question 17: Does the Division concur:

- a. that the proposal to provide narratives for all subjects discontinuing due to *Other, Physician Decision, and Patient Decision* addresses the recommendation and will be adequate for filing and review of the applications?**

Yes.

Meeting Discussion: There was no discussion.

- b. with the proposed list of adverse events of interest for which narratives are written?**

(b) (4)
You should create a list of events that are more targeted, and explain why such events were selected.

Meeting Discussion: UCB noted that the hypertext link was incorrect and notes that it provided the corrected list of events of interest in an email dated July 28, 2014. UCB requested post-meeting feedback regarding this list. DNP agreed to provide feedback in a post-meeting note.

Post-meeting Note: UCB notes that it will include torsades de pointes. However, any significant cardiac arrhythmia should be included. Episodes of syncope or presyncope and significant alterations in blood pressure should also be included. This is particularly important for intravenous infusions. While the documentation of the chronology of these events is very important (e.g., noting the time such events occurred in relation to initiation of treatment), this is particularly important with the intravenous studies, where the chronology has to be more detailed (observations during infusion and time after infusion, in minutes and hours).

c. with the proposed format and placement of the requested index listing all submitted narratives with links?

Yes. In addition, it would be helpful if all narratives were included in a single searchable pdf document.

Meeting Discussion: UCB noted it will provide narratives in a single searchable document, provided the size meets ESUB limitations. The ESUB representative noted that the megabyte limits have been substantially increased (i.e., now as large as 400 megabytes).

Question 18: Does the Division concur:

a. the plan for submission of CRFs is acceptable?

Yes.

Meeting Discussion: There was no discussion.

b. that the proposed narrative index plan to hyperlink CRFs to the corresponding narrative is adequate and a separate CRF index is not required?

Yes, but also see answer to Question 17c.

Meeting Discussion: The Division clarified that the reference here to 17c refers to the Division's request to provide all narratives in a single pdf. All CRFs are not expected to be provided as a single document. CRFs should be hypertext linked to narratives.

Question 19: Does the Division concur that the planned format for datasets is adequate to support filing and review of the applications?

Statistics

For detailed instructions regarding submitting efficacy datasets and related documentation, please refer to Study Data Specification 2.0 (July 18, 2012).

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>

Clinical

The plan is acceptable provided that the mapping from the raw data (CRFs) to the SDTM datasets is submitted. Also the SDTM formatted datasets should be submitted for the ISS (in addition to the ADaM-formatted datasets). Please refer to the CDER Study Data Specifications Document and the Data Standards Common Issues Document at the FDA's website. Please provide a Study Data Reviewer's Guide for the SDTM datasets.

Meeting Discussion: In regard to the issue that the SDTM formatted datasets be submitted to the ISS in addition to the ADaM dataset, UCB plans on providing individual study SDTM datasets. Thus, SDTM datasets will not be integrated. The integrated ISS ADaM datasets will be traceable to the individual study analysis datasets and/or the individual study SDTM datasets. Supporting ISS documentation (e.g., define files) will trace from the individual study-level datasets to the integrated ADaM datasets. UCB asked if this is acceptable and if UCB needs to construct an integrated SDTM dataset?

Post-meeting Note: Yes, the Division requests that UCB submits an integrated SDTM dataset.

Question 20: Does the Division concur that such datasets as described in the referenced draft guidance are not required to support filing and review of the application?

The datasets described in the referenced draft guidance are voluntary. Please refer to the Office of Scientific Investigations' additional comment in Section 3.0 ADDITIONAL COMMENTS of this document.

Meeting Discussion: There was no discussion.

Question 21: Does the Division concur with:

a. the proposed clinical data cutoff date of 01 October 2014?

Yes.

Meeting Discussion: There was no discussion.

b. the plans for providing the 120 Day Safety Update?

Yes.

Meeting Discussion: There was no discussion.

c. the plans for the dataset to be included in the 120 Day Safety Update?

Yes.

Meeting Discussion: There was no discussion.

3.0 ADDITIONAL COMMENTS

Clinical Pharmacology

The Drug Interaction Guidance has updated since you initiated the clinical development of brivaracetam. You should conduct in-vitro studies to determine whether BRV and its major metabolites are substrates of major transporters (e.g., BCRP, OAT1, OAT3, or OCT2) and their inhibition potential of these transporters. Please refer to the current drug interaction guidance for additional details

<<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>>

Meeting Discussion: UCB indicated that it has already completed the aforementioned in-vitro transporter studies in response to the release of the updated drug interaction guidance. The results of these in-vitro studies will be provided in the NDA submission.

Office of Scientific Investigations

Electronic submission of the following requested information **is voluntary**. The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

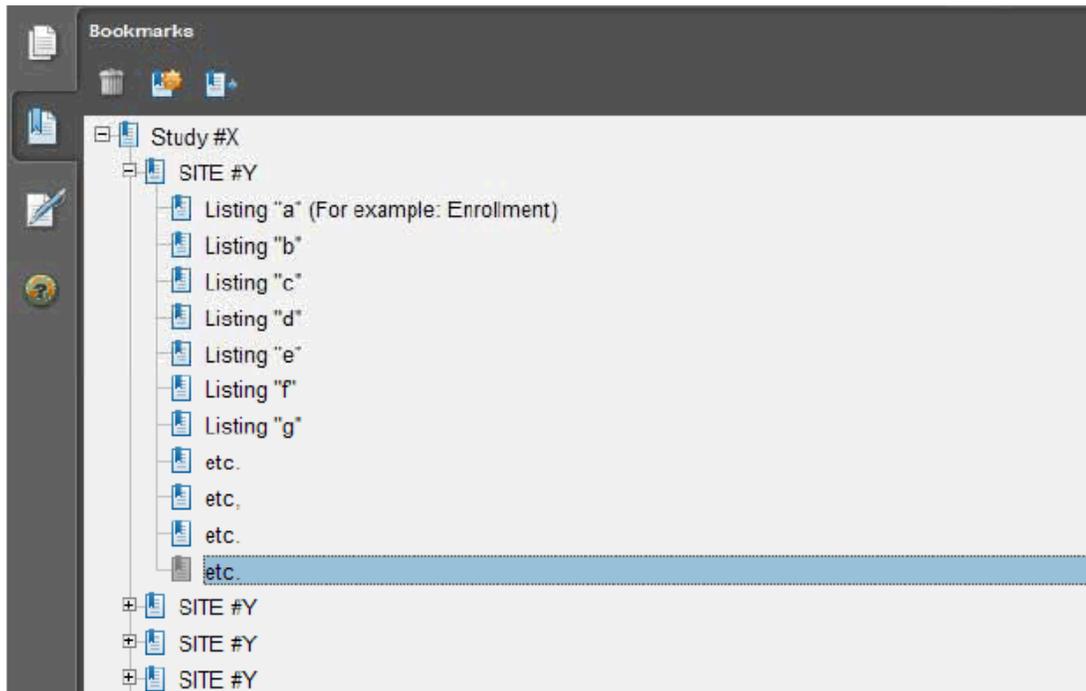
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Meeting Discussion: There was no discussion.

4.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 3, 2014, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG

will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time, the Agency does not feel that a REMS will be necessary, however the team will make a final determination for the need of a REMS during the review of the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 - the exploration of the relationship between exposure and safety for pertinent adverse events.

Prominently identify each submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential

and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Appendix 1. CSS provided Abuse-related AE terms

All clinical studies should be evaluated for indicators of abuse potential. The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA 12.0 dictionary as well as frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes are key observations that may influence the assessment of abuse potential and a recommendation for scheduling. However, all data submitted in an NDA are critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-related terms:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as “high blood pressure,” etc.)

Elevated mood: mood elevated, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation.

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic terms:

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia.

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

Euphoria-related terms:

Euphoric mood

(* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)

Elevated mood

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Feeling abnormal
Feeling drunk
Feeling of relaxation
Dizziness
Thinking abnormal
Hallucination
Inappropriate affect

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence
Mood disorders and disturbances
Mental impairment disorders
Drug tolerance
Habituation
Drug withdrawal syndrome
Substance-related disorders

Dissociative/psychotic terms:

Psychosis
Aggressive
Confusion and disorientation

Other terms:

Suicidal ideation/behavior
Committed suicide
Homicidal ideation/behavior
Homicide

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Please see Section 5.0 Action Items

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Post-meeting feedback for e-mail response to Preliminary Comment for Question 17 b	FDA	August 28, 2014
Post-meeting feedback for Question 19	FDA	August 28, 2014
Post-meeting feedback from CSS Question 9 re: providing an example of a CSS review that is readily available to the public on the Internet	FDA	August 28, 2014

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6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

WILLIAM H Dunn
08/27/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,205

UCB, Inc.
Attention: Kristen Piatak
Regulatory Affairs Manager
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for brivaracetam capsules.

We also refer to the meeting between representatives of UCB, Inc. and the FDA on December 11, 2006. The purpose of the meeting was to discuss the development of brivaracetam to treat epilepsy.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure: meeting minutes



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: December 11, 2006
Meeting Type: Type B
Meeting Category: EOP2
Meeting Location: White Oak Bldg #22, Room 1315
Application Number: IND 70,205
Product Name: brivaracetam
Received Briefing Package: November 13, 2006
Sponsor Name: UCB, Inc.
Meeting Requestor: Kristen Piatak, Regulatory Affairs Manager
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., Medical Team Leader
Norman Hershkowitz, M.D., Ph.D., Medical Reviewer
Lois Freed, Ph.D., Supervisory Pharmacologist
Kathleen Young, Ph.D., Pharmacology Reviewer
Susan Daugherty, Regulatory Project Manager

Division of Biometrics II

Kun Jin, Ph.D. Statistical Team Leader

Division of Pharmaceutical Evaluation

Sally Yasuda, Pharm.D., Clinical Pharmacology Reviewer

Division of Pre-Marketing Assessment I

Martha Heimann, Ph.D., Pharmaceutical Assessment Lead

External Attendees:UCB, Inc.

Deborah Hogerman, B.A., Director, US Regulatory Affairs

Kristen Piatak B.A., R.A.C., Manager, Global Regulatory Affairs

Sherri N. Thrower, B.S., Associate CMC, Global Regulatory Affairs

Anne Danniau, A.M., Statistical Team Leader, Allergy/Oncology/CNS

Paul Meyvisch M.Sc. Senior Statistician, Neurology/Psychiatry, Biometrics

Armel Stockis, M.Sc, Ph.D., Head of Pharmacometrics, Clinical Pharmacology and Experimental Medicine

Maria Laura Sargentini-Maier, Pharm.D., Ph.D., Head of Pharmacology Modeling & Simulations, Clinical Pharmacology and Experimental Medicine

Geoffrey Rose Ph.D, Head Product Safety & Metabolism, Nonclinical Development

Michele Leonard, Ph.D., Senior Principal Scientist, Regulatory Safety, Nonclinical Development

Peter Verdru, M.D., Vice President, Clinical Research, Head of Neurology/Psychiatry

Philipp von Rosenstiel, M.D., Clinical Program Director, BRV, Neurology/Psychiatry

Ursula Falter, Ph.D., Principal Clinical Project Manager, Neurology/Psychiatry

Christine de la Loge, MSc., Senior Patient Reported Outcomes Specialist, Health Outcomes Research

1.0 BACKGROUND

IND 72,205 for brivaracetam was submitted on July 12, 2004 for the treatment of epilepsy. Brivaracetam is a new chemical entity that is structurally related to piracetam and levetiracetam.

On July 29, 2005, UCB submitted two carcinogenicity special protocol assessments. Minutes from the subsequent Executive Carcinogenicity Assessment Committee minutes were faxed to the sponsor on September 8, 2005.

(b) (4)

The purpose of today's meeting is to discuss the Phase 3 development of brivaracetam as adjunctive therapy in the treatment of partial onset seizures (b) (4) in adults with epilepsy.

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

2.0 DISCUSSION

Responses to questions from UCB, Inc. regarding the development of brivaracetam

Question #1 (CMC):

Does the Division concur that [REDACTED] (b) (4)
[REDACTED] are starting materials?

FDA Response:

Yes.

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

Question #2 (CMC):

Does the Division concur that the BRV drug substances produced by [REDACTED] (b) (4)
are equivalent?

FDA Response:

This will be a matter for review. [REDACTED] (b) (4)

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

Question #3 (CMC):

Does the Division concur that the test methods and specifications proposed for the drug substance and drug product are satisfactory as presented for this stage of development and eventual registration?

FDA Response:

The proposed tests appear appropriate; however suitability of the proposed acceptance criteria will be determined during review of the application. We note that the specifications currently reference European Pharmacopeia (Ph. Eur.) analytical procedures and acceptance criteria (e.g., for uniformity of content, microbiological quality). Although we will accept submission of Ph. Eur. tests; you will need to show that the tests provide for equivalent or better assurance of quality versus the corresponding USP tests.

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

Question #4 (CMC):

Does the Division concur that the stability programs presented for BRV drug product are sufficient for this stage of development and eventual registration?

FDA Response:

The stability programs described in the briefing package are adequate to support Phase 3 trials. The information provided is inadequate to allow us to determine whether the stability programs are sufficient to support an NDA filing. In order for the Agency to provide feed back on suitability for an NDA submission, you will need to provide additional specific details, e.g., batch scales, proposed commercial packaging, stability test parameters.

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

Question #5 (Clinical Pharmacology):

Is UCB's plan to examine the potential impact from use of (b) (4) in the formulation acceptable to the Division? UCB plans to then submit the results of this investigation in the first NDA filing for BRV –does the Division concur?

FDA Response:

Yes, this is acceptable.

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

Question #6 (Clinical Pharmacology):

Does the Division concur with the proposed bridging strategy which includes performing comparative dissolution and a bioequivalence study?

FDA Response:

No. You base this proposal on BRV meeting requirements for BCS class I. However, there is insufficient information to make this determination. The following data should be submitted: 1) dissolution in (b) (4), 2) raw data and dissolution curves for all dissolution studies, 3) solubility data, 4) data to support stability in the gastrointestinal tract pH, and pKa and partition coefficient. The results of the in vitro permeability studies will be helpful when they are completed. If the relevant information is submitted, it could be reviewed within several weeks to make a determination regarding BCS class I.

(b) (4)

Discussion

The sponsor reported that they have conducted an absorption study (pharmacoscintigraphic study) and those results demonstrated [REDACTED] (b) (4). With this study in mind, the sponsor asked if in vitro studies would have to be conducted as well.

As a post-meeting note, this may be supportive [REDACTED] (b) (4).

Question #7 (Nonclinical):

Is UCB's proposed testing strategy for the safety of metabolite 107092-1 acceptable to the Division?

FDA Response:

Yes, except for the following:

- 1. You only need to test the general toxicity of metabolite 107092-1 in one species, unless findings in that species warrant further testing in a second species. Selection of species should be justified in the study report. Dose selection for the 4- and 13-week toxicity studies should ensure that the high dose is associated with overt toxicity or demonstrated to be a maximum feasible dose, rather than some multiple of human exposure.**
- 2. We recommend that the pharmacological activity of metabolite 107092-1 be characterized.**
- 3. A study to evaluate potential adverse effects of ucb-107092-1 on embryo-fetal development should be conducted in one species.**

The need for additional toxicology studies of 107092-1 will be determined based on the available data on the metabolite and on ucb 34714.

Discussion

The Sponsor agreed to conduct the program as outlined by the Division. The general toxicity study of metabolite 107092-1 is to be conducted in rat. Based on data to date, no pharmacological activity has been identified for metabolite 107092-1.

Question #8 (Nonclinical):

[REDACTED] (b) (4)

FDA Response:

- * **As a new chemical entity, brivaracetam will need to be assessed for abuse liability.**
- * **According to 21 CFR § 314.50 (5) (vii), the Abuse Potential Section of an NDA includes the following:**
 - Proposal for scheduling and all scientific data that forms the basis of the proposal**
 - Abuse Potential Assessment:**
 - * **Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)**
 - * **Pharmacokinetics and pharmacodynamic (including full data on receptor binding)**
 - * **Primary data from abuse potential studies in animals and humans**
 - * **Adverse events in clinical studies related to abuse potential**
 - * **Integrated summaries of safety and efficacy (ISS and ISE)**
 - * **Information related to overdose**
 - * **Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies**
- * **You may submit protocols for animal abuse liability studies to CSS prior to their initiation, in order to determine whether the studies are adequately designed. The rat is an acceptable model for receptor binding, drug discrimination and self-administration studies.**
- * **Depending on the results of nonclinical and clinical studies, a human abuse liability study may be necessary.**

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

Question #9 (Nonclinical):

Juvenile Safety Program

a) Does the Division concur with the proposed design and dose levels chosen for the nonclinical juvenile toxicity study in the rat?

FDA Response:

The proposed design and dose levels chosen for the juvenile toxicity study in rat appear to be acceptable; however, a final determination as to the adequacy of the study will be based upon review of the data.

b) Does the Division concur with the planned timing of the nonclinical juvenile toxicity study in rats in parallel with the first pediatric clinical trial?

FDA Response:

You will also need to conduct a juvenile study in non-rodent (generally, the dog). The age of the animals and the duration of dosing should be appropriate to the intended clinical use and, in addition to the standard parameters, should include the following:

- 1. A neurological examination toward the end of the treatment period (prior to the last dose) and at the end of an adequate recovery period following cessation of dosing.**
- 2. Bone densitometry**
- 3. Expanded CNS, cardiovascular and reproductive organ histopathological examinations with particular attention to alterations indicative of developmental insult, in addition to the routine examination of a standard battery of tissues, at the end of the treatment and recovery periods.**

Study reports for the juvenile studies should be submitted prior to repeat-dose clinical trials in children less than 13 years of age.

Discussion

The Sponsor proposed to start the clinical program after data from the juvenile rat study have been submitted and to conduct the dog study concurrent with the human studies. The Division did not agree with this proposal due to the limited previous human experience with brivaracetam. Juvenile studies in both rat and dog need to be submitted prior to initiation of repeat-dose clinical trials. However, the Sponsor may attempt to justify initiating such a clinical trial without juvenile studies in two species based on available clinical and nonclinical (i.e., completed juvenile rat study and dose-range finding study in juvenile dog) data.

Question #10 (Clinical/Clinical Pharmacology):

Does the Division concur with the selected dose range to be explored in the confirmatory studies?

FDA Response:

Examination of your pharmacodynamic modeling analysis and individual studies indicates that the planned dose range is probably appropriate. Because of some disparity in Phase 2 trials there is some concern that the upper range has not been completely explored. Thus, study N01114, which examined doses in the upper range (50 and 150 mg/day), found a rather small therapeutic effect when compared to effects observed in study N01193. (b) (4)

(b) (4)

It is a general impression that a greater degree of intolerance is observed in the upper therapeutic range for anticonvulsant: i.e. these agents have a narrow therapeutic window. The division therefore wonders whether the upper limit of the range should be increased (e.g. to 150 or 200 mg/day).

Discussion

The sponsor stated that,

(b) (4)

The division re-iterated their stated concerns, but agreed that these are suggestions and are not obligatory.

Question #11 (Clinical):

Does the Division concur:

a) with the design and duration of treatment proposed for the pivotal trials (N01252 and N01253)?

FDA Response:

The general design and duration are appropriate.

Discussion

Response accepted as presented by the Sponsor. They asked whether, considering similarity of mechanisms of agents, whether the use of brivaracetam adjunctively with levetiracetam should be included.

(b) (4)

The Division raised the concern that the proposal to use brivaracetam with levetiracetam may possibly interfere with the ability to demonstrate an effect of brivaracetam.

(b) (4)

b) with the proposed stratification?

FDA Response:

The present stratification plan appears adequate. However, we also expect that you will look at patients sub-grouped by the concomitant anticonvulsants used, in order to confirm that therapeutic effect is independent of concomitant anticonvulsant (especially relevant for CBZ). Examination of PHT and CBZ concentrations may be helpful as well.

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

c) with UCB's proposal not to adjust dose levels of the concomitant AEDs CBZ and PHT?

FDA Response:

The division agrees that dose level of CBZ and PHT should not be altered.

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

d) with UCB's proposal to immediately administer doses of 5 mg/day, 20 mg/day, 50 mg/day or 100 mg/day without prior up-titration?

FDA Response:

This may be acceptable, but a thorough analysis presenting adverse event incidence for patients started on high doses without titration is not presented in any detail to allow the division to provide any meaningful feedback. These data should be provided.

Discussion

The Sponsor presented information regarding numbers of patients who have been exposed to high doses without titration and who tolerated dosing well: e.g. at least 18 patients who were exposed to 100 mg without titration exhibited no major problems with tolerability. The division agreed that the regimen may be adequate but asked the Sponsor to provide a more carefully outlined justification for this dosing regimen. The Sponsor agreed.

Question #12 (Clinical):

Are the described study population and the proposed geographical regions for study sites acceptable to the Division?

FDA Response:

Only one study will examine a North American population. It would be important to have an adequate number of patients in this stratum of the study (e.g., at least 80) from North America (Canada and US).

With regard to inclusion criteria you are permitting the use of hormonal contraception (high dose with strong enzyme inducing concomitant anticonvulsants). We usually ask for a barrier method combined with hormonal treatment because of the potential for drug-drug interactions. Unless there is good evidence of a lack of such interaction, hormonal contraception alone should not be permitted.

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

Question #13 (Clinical):

Efficacy - For the proposed pivotal trials (N01252 & N01253), does the Division concur:

a) with the proposed primary efficacy variable?

FDA Response:

The primary endpoint is acceptable.

Parts B, C D and E: The division uses the following general guidelines for labeling of secondary endpoints: 1) a demonstration that the endpoint has adequate reliability and validity, 2) a demonstration that the effect is independent of the effect of the drug on the primary endpoint, i.e. the effect is in a completely independent domain, 3) the effect should be replicated in a separate study, 4) there must be correction for an overall type 1 error.

With this in mind what follows are the answers to specific questions:

[Redacted block] (b) (4)

FDA Response:

No. [Redacted block] (b) (4)

Discussion

[Redacted block] (b) (4)

c) that the QOLIE 31-P is an appropriate tool to assess the beneficial effects of AEDs on HRQoL for epilepsy subjects and in particular, on subjects' seizure related worries and daily activities?

FDA Response:

Insufficient information has been provided to the division to determine whether this is an appropriate measure of quality of life improvement following anticonvulsant treatment in epilepsy patients (also see part D of this answer).

Discussion

See discussion under d), below.

[Redacted] (b) (4)

FDA Response:

[Redacted] (b) (4)

Discussion

The division noted that these endpoints appear likely to be highly correlated with the primary endpoint. [Redacted] (b) (4)

[Redacted] *In addition, more information needs to be provided on the validity of such endpoints (e.g., as stated above, what magnitude change constitutes a clinically meaningful change). The sponsor will provide information to support the use of QOLIE as a secondary measure using either Phase 2 or Keppra data.*

[Redacted] (b) (4)

(b) (4)

The sponsor will submit supporting documentation to their IND.

Question # 14 (Statistical):

Does the Division concur that:

- a) the assessment of efficacy of (b) (4) mg/day can be based on statistical superiority for only one trial?

FDA Response:

Generally the statistical significance in two independent studies is required for the labeling of a dose. The division, however, would be open to an argument, based upon experience in all 3 controlled studies, that labeling should be granted for this dose.

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

b) (b) (4) ?

FDA Response:

No.

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

Question #15 (Clinical):

Does the Division concur that the Study N01254 design (which includes both localized and generalized epilepsy patients) is appropriate to fulfill the primary objective of providing additional safety and tolerability data for BRV in the targeted indication and in the relevant dose-range?

FDA Response:

Yes, assuming doses studied in this flexible dose study are generally similar to those approved for treatment based upon the fixed dose studies.

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

Question #16 (Clinical):

(b) (4)

(b) (4) ?

FDA Response:

We are a little uncertain as to what you mean by supportive evidence, but, the results of this study will be examined and may assist the division in its final decision.

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

Question #17 (Clinical):

(b) (4)



If you wish to gain such a claim, you should submit a prospective plan for an appropriate analysis. Typically, we would require replication of such a finding, but we are open to an argument that a pooled analysis might be acceptable.

Discussion

The sponsor will submit their statistical analysis plan for review.

Question #18 (Clinical):

Does the Division concur that, in the light of the safety and tolerability profile of BRV known to date, the proposed safety variables are sufficient to adequately assess the safety of BRV in the proposed indication?

FDA Response:

It should be noted that along with lipid screen and microscopic UA, uric acid is missing. Without actually reviewing this information the division cannot argue that you should continue to monitor such labs. If appropriate these labs may be monitored less frequently.

Discussion

The sponsor will include uric acid monitoring in their Phase 3 trials. The division suggested that such labs be drawn at about 7, 10 and 12 weeks as well as 6 months to one year. The sponsor proposes to monitor the microscopic urinalysis in patients with abnormal urine chemical analysis and continue these patients in Phase 3. The Division agreed in part with this proposal. However, DNP believes microscopic urinalysis can be dropped only after results have been performed in a reasonable number of patients; if the results from a reasonable sample of patients are acceptable, then the sponsor can initiate their plan to only check microscopic analysis in patient with abnormal chemical screen.

Question #19 (Clinical):

Does the agency concur with UCB's proposal to perform only local ECGs in the proposed pivotal studies, given the absence of a QTc prolongation effect in a thorough QT study?

FDA Response:

This QT study has not been reviewed nor does it appear in your submission (it is noted in the listings as "ongoing and follow-up"). Examination of the submission indicates

It is assumed that you are inquiring as to whether this plan is adequate. This division would argue that other cardiac problems, unrelated to QT can occur and the simple absence of QT prolongation is not adequate to obviate all monitoring. We would therefore suggest more frequent monitoring than is indicated. For example, in the controlled trials, EKG monitoring could be performed at 2 weeks and 2 months following drug initiation as well as at the final dose. Monitoring may be performed approximately at 6 month or longer in the extension trials. Monitoring at a local level is adequate. The EKG reading need not be centralized.

Discussion

The sponsor will submit the QT study data for review.

(b) (4)
The Division recommends conducting EKGs at baseline, 4 weeks, 12 weeks, at the end of the trial and at 6 months or during the open-label extension phase of the trial. Significant abnormalities (e.g. adverse events) and outliers would need to be reported.

Question #20 (Clinical):

Does the Division concur that the planned extent of exposure is adequate to support the safety for registration?

FDA Response:

Yes.

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

Question #21 (Clinical):

Does the Division concur:

a) that the proposed doses (b) (4) selected for the pediatric PK Study N01263, are acceptable?

FDA Response:

This seems reasonable, although every effort should be made to ensure that the maximal tolerated dose (MTD) is achieved to optimize dosing in the pivotal studies and that the full range of tolerable doses should be explored, including lower doses.

Discussion

The sponsor reports that it has been difficult to find a MTD in adults. The

(b) (4)
The Division does not agree with this approach. Instead, the Division would like to see a full range of doses studied in the pediatric population. In addition, if the sponsor wishes to receive pediatric exclusivity, the Division would want the studies to optimize the possibility of demonstrating an effect in children.

b) with the age categorization for Study N01263?

FDA Response:

The age distribution within each age group should be relatively evenly distributed.

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

c) that the start of the BRV clinical pediatric development in epilepsy on the basis of the current clinical data in adults is acceptable?

FDA Response:

A small clinical development program is acceptable at this time. An argument can be made that greater exposures in pediatrics should await confirmation of efficacy in adults.

Discussion

(b) (4)
he sponsor will submit a proposal to their IND. The Sponsor noted that they will meet with the division prior to the initiation of the pediatric trial.

Question #22 (Clinical):

FDA Response:

See response to Question #8.

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

Additional Clinical Pharmacology Comments:

1. **You should justify the relevance of the Phase 1 clinical pharmacology studies to the proposed doses for clinical use. You should also justify how the food effect study is applicable to the proposed Phase 3 and commercial product. As we have previously advised, a food effect study should be performed on the highest strength of the to-be-marketed formulation.**

Discussion

The sponsor will repeat the food effect arm will be with the to-be-marketed formulation.

2. **You should provide information as to whether the metabolites are pharmacologically active (efficacy or toxicity).**

Discussion

The sponsor will submit this information to the IND.

Additional Nonclinical Comments:

The high doses in the 6-month toxicity study in rat (450 mg/kg/day) and the 39-week toxicity study in monkey (900 mg/kg/day) are no-adverse-effect levels, i.e., no dose-limiting toxicity was observed. Higher daily doses (up to 700 mg/kg/day) are being used in the ongoing carcinogenicity study in rat, which may provide sufficient chronic data in this species. We are not aware of data in monkey at higher doses, or data demonstrating that the dose of 900 mg/kg/day is a maximum feasible dose. Therefore, you need to further justify the high dose used in the chronic monkey study. If substantially higher doses can be achieved in monkey, the chronic study may need to be repeated.

There was no further discussion regarding these comments at the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

The sponsor would like to meet with the Division in the first half of next year to discuss the pediatric studies.

4.0 ACTION ITEMS

The sponsor will submit their Phase 3 protocols for review and comment.

5.0 ATTACHMENTS AND HANDOUTS

The sponsor used one handout during the discussion at this meeting and it is attached.

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

**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

1/18/2007 03:34:33 PM

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205836
NDA 205837
NDA 205838

LATE-CYCLE MEETING MINUTES

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

Attention: Deborah Hogerman
Vice President, Regulatory Affairs

Dear Ms. Hogerman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: BRIVIACT (brivaracetam); 10, 25, 50, 75, and 100 mg oral tablets; injection (10 mg/mL); and oral solution (10 mg/mL)

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 29, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathy Michaloski, Sr. Regulatory Project Manager at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Norman Hershkowitz, MD, PhD
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 29, 2015, 10:00 – 11:00 am EST
Meeting Location: White Oak Building 22 Room 1419
Application Number: NDA 205836 oral tabs
NDA 205837 IV
NDA 205838 oral soln
Product Name: BRIVIACT (brivaracetam)
Indication: adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy
Sponsor/Applicant Name: UCB, Inc.
Meeting Chair: Norman Hershkowitz, MD, PhD
Meeting Recorder: Cathleen Michaloski, BSN, MPH, RAC

FDA ATTENDEES

Ellis Unger, MD, Director, ODE I
Billy Dunn, MD, Director, DNP
Norman Hershkowitz, MD, PhD, Team Leader Clinical, DNP
Steven Dinsmore, DO, Clinical Reviewer, DNP
Sally Yasuda, PharmD, Safety Team Leader, DNP
Mary Doi, MD, MS, Safety Reviewer, DNP
Sharon Yan, PhD, OTS/OB
Andrei Ponta, PhD, chemist, ONDP/Division 1
Michael Bewernitz, PhD, OTS/OCP/DCP1
Robert Pratt, PharmD, DRISK
Karen Long, PharmD, DPPV
Ebern Dobbin, CQA, OPF/DIA
Justine Harris, RPh, DMEPA
Okpo Eradiri, PhD, ODNP/DBP
Kun Jin, PhD, Team Leader, Biostatistics
Cathy Michaloski, BSN, MPH, Project Manager, DNP

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor, ERG

APPLICANT ATTENDEES

Elena W. Cleary, PhD, Mission Lead, Epilepsy - UCB Meeting Chair
Laurence Leonardy, Director, Global Regulatory Affairs
Alison Parks, Associate Director, US Labeling, Advertising and Promotion
John Whitesides, PhD, Senior Clinical Program Director

Jimmy Schiemann, MD, Senior Medical Director
Belinda McDonough, MB BCh BAO, Director Safety Lead (CNS), Patient Safety
Armel Stockis, PhD, Senior Director, Clinical Pharmacology CNS
Martin E. Johnson, MS, Principal Biostatistician
Phyllis Smetana, Project Statistical Programmer
Deborah Hogerman, Vice President, Regulatory Affairs, UCB
Michelle Morgan-Adams, Regulatory Affairs Manager

1.0 BACKGROUND

NDA 205836, NDA 205837, and NDA 20583 were submitted on November 20, 2014, received, November 20, 2014, for BRIVIACT (brivaracetam).

Proposed indication: adjunctive treatment of partial onset seizures (POS) in patients 16 years or older with epilepsy

PDUFA goal date: November 20, 2015.

FDA issued a Background Package in preparation for this meeting on July 16, 2015.

2.0 DISCUSSION

LCM AGENDA

1. Introductory Comments
2. Discussion of Substantive Review Issues

Each issue will be introduced by FDA and followed by a discussion.

The following safety information requests are considered important for successfully completing the NDA review and are presently remain pending:

- the complete assessment of the 120-day Safety Update datasets for all pooled groups;
- the assessment of the ISS datasets for pooled groups other than Pools S1 through S4;
- the correction of the identified algorithm issues; and
- the submission of corrected ISS datasets (and 120-day Safety Update datasets, if applicable) with updated AE summary tables and updated narratives (if applicable).

The sponsor should refer to the corresponding data requests for further information.

DISCUSSION:

Regarding your question on re-performing analyses using the corrected algorithms for the 120-day Safety Update datasets, analyses should be rerun for all pooled groups with LTFU studies in addition to Pool S4 (e.g., Pool Pediatric). The revised tables for Pool S4 should be submitted first.

As already requested, the revised datasets (both ISS and 120-day Safety Update datasets) should include the same variables as the original datasets and the algorithms provided in the original submission (“algorithm-iss”) and for the 120-day Safety Update (“algorithm-120day”) should apply to these revised datasets.

The Division noted that the requested and pending information is rather significant in volume; this may necessitate the extension of the review clock.

3. Discussion of Minor Review Issues

A determination of the efficacy for the 50 mg dose is under evaluation because of the potential pharmacodynamic confounding effects of concomitant levetiracetam use and pharmacokinetic induced increases in the carbamazepine 10-11 epoxide observed in studies 1252 and 1253.

DISCUSSION:

No significant discussion.

4. Additional Applicant Data

- See item number 2 for pending safety data.

DISCUSSION:

See item number 2.

5. Information Requests

The following safety information requests remain pending:

- algorithmic issues for safety datasets (see item number 2 above; IR sent June 5th);
- autopsy report (pt #07151, IR sent March 30th);
- analyses for falls/injuries (IR sent June 15th); and
- Hy’s Law/DRESS analyses (IR sent June 22nd).

Efficacy dataset request regarding the use of CBZ in subpopulations of patients from pivotal trials (IR July 14, 2015).

DISCUSSION:

The Division noted that CBZ datasets were received.

Post Meeting note: Efficacy data sets regarding the use of CBZ were received on July 20, 2015.

6. Postmarketing Requirements/Postmarketing Commitments

PREA PMRs will require the sponsor to perform clinical studies to examine the pharmacokinetics, efficacy, and safety of brivaracetam in the pediatric population of 1 month and above.

DISCUSSION:

It was noted that draft labeling and any PMR/PMCs are expected to be communicated to you by September 20, 2015. There will be pediatric post market requirements.

7. Major labeling issues

At present none are identified, but review of the above issues may necessitate some changes in the label.

DISCUSSION:

See number 6 above.

8. Review Plans

Whether review of the pending information requests regarding the safety datasets extend the review clock will be determined after receipt of the information.

DISCUSSION:

The Division noted that at this point we can confirm that there will be pediatric postmarket requirements under PREA

Additional Comment:

The sponsor inquired as to the status of the CSS review. The Division noted that we were not aware of any identified issues.

Post-meeting comment: The Controlled Substance staff (CSS) review is on-going. We have been informed that the review is nearing completion but is still with the Agency. However, it should not be long before the review goes to the DEA. We will keep you informed as new information becomes available.

Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

NORMAN HERSHKOWITZ
08/13/2015



NDA 205836
NDA 205837
NDA 205838

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

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

Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs

Dear Ms. Piatak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: BRIVIACT (brivaracetam); 10, 25, 50, 75, and 100 mg oral tablets; injection (10 mg/mL); and oral solution (10 mg/mL)

We also refer to the Late-Cycle Meeting (LCM) teleconference scheduled for July 29, 2015, at 10:00 am EST. Attached is our background package, including our agenda, for this meeting.

If you have any questions, contact Cathy Michaloski, Sr. Regulatory Project Manager, by email at Cathleen.michaloski@fda.hhs.gov or by phone at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: July 29, 2015, 10:00 – 11:00 am EST
Meeting Location: White Oak Building 22 Room 1419
Application Number: NDA 205836
NDA 205837
NDA 205838
Product Name: BRIVIACT (brivaracetam)
Indication: adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy
Sponsor/Applicant Name: UCB, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

CLINICAL SAFETY:

The following safety information requests are considered important for successfully completing the NDA review and presently remain pending:

- the complete assessment of the 120-day Safety Update datasets for all pooled groups;
- the assessment of the ISS datasets for pooled groups other than Pools S1 through S4;
- the correction of the identified algorithm issues; and
- the submission of corrected ISS datasets (and 120-day Safety Update datasets, if applicable) with updated AE summary tables and updated narratives (if applicable).

The sponsor should refer to the corresponding data requests for further information.

LCM AGENDA

1. Introductory Comments – 5 minutes (Norman Hershkowitz, MD, PhD, CDTL/ Cathy Michaloski, BSN, MPH, RPM)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion.

The following safety information requests are considered important for successfully completing the NDA review and presently remain pending:

- the complete assessment of the 120-day Safety Update datasets for all pooled groups;
- the assessment of the ISS datasets for pooled groups other than Pools S1 through S4;
- the correction of the identified algorithm issues; and
- the submission of corrected ISS datasets (and 120-day Safety Update datasets, if applicable) with updated AE summary tables and updated narratives (if applicable).

The sponsor should refer to the corresponding data requests for further information.

3. Discussion of Minor Review Issues – 5 minutes

1. A determination of the efficacy for the 50 mg dose is under evaluation. The Division is exploring the potential pharmacodynamic effects of concomitant levetiracetam use and

increases induced by brivaracetam in the carbamazepine (CBZ) 10-11 epoxide observed in studies 1252 and 1253.

4. Additional Applicant Data – 5 minutes

- See item number 2 for pending safety data.

5. Information Requests– 10 minutes

The following safety information requests remain pending:

- algorithmic issues for safety datasets (see item number 2 above; IR sent June 5, 2015);
- autopsy report (patient #07151, IR sent March 30, 2015);
- analyses for falls/injuries (IR sent June 15, 2015); and
- Hy's Law/DRESS analyses (IR sent June 22, 2015).

Also pending are the requested efficacy datasets describing the use of CBZ in subpopulations of patients from pivotal trials (IR July 14, 2015).

6. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

PREA PMRs will require the sponsor to perform clinical studies to examine the pharmacokinetics, efficacy, and safety of brivaracetam in the pediatric population of 1 month and above.

7. Major labeling issues – 5 minutes

At present none identified, but review of the above issues may require changes in labeling.

8. Review Plans – 5 minutes

Whether submission of the data referenced in the pending information requests will be considered a major amendment will be determined after receipt of the information.

9. Wrap-up and Action Items – 5 minutes (Chair will summarize any outstanding action items)

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/s/

WILLIAM H Dunn
07/16/2015