CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206030Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206030 SUPPL # N/A HFD # 120

Trade Name Carnexiv

Generic Name carbamazepine injection, for intravenous use

Applicant Name Lundbeck, LLC

Approval Date, If Known October 7, 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 ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

Study OV-1015 is a bioavailability study and both studies, OV-1015 and 13181A, are safety studies. Per the clinical pharmacology primary review, "Sponsor conducted a comparative PK study (OV-1015) as well as a safety study (13181A where PK data were not collected) to support approval. Study OV-1015 compared steady state oral CBZ pharmacokinetics in epilepsy patients with the pharmacokinetics of an intravascular infusion of 70% of the total 24-hour oral dose administered every 6 hours. In addition, Sponsor characterized the PK of Captisol (the Carbella solubizing agent) in study OV-1015."

Also, according to the sponsor's original submission on December 23, 2013, in Table 1 found in Module 2.7.2, "*Summary of Clinical Pharmacology Studies*," the sponsor states that study OV-1015 is 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:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Three years (Hatch Waxman)
Seven years (Orphan Designation) – See sponsors December 23, 2013 module 1.3.5.3 request for market exclusivity.

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA 020712
NDA 018927
NDA 020234
NDA 021710
NDA 016608
NDA 018281

2. Combination product. – N/A

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 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:

The studies conducted under this application were open label studies to determine safety.

(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:

NDA 016608 , Tegretol	*FDA's previous finding of safety and effectiveness: Nonclinical pharmacology; Nonclinical pharmacokinetics; and Nonclinical toxicology (Genotoxicity; Carcinogenicity; Other toxicity evaluation); In vitro studies using human biomaterial; Clinical Efficacy for proposed indications; and Clinical Safety (from label)*
NDA 020234, Tegretol XR	*FDA's previous finding of safety and effectiveness: Clinical pharmacology; Clinical Efficacy for proposed indications; and Clinical Safety (from label)*

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"): N/A

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?

N/A because Question 3(c) is also N/A (i.e., no investigations are listed)

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? N/A

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: E. Andrew Papanastasiou
Title: Regulatory Project Manager
Date: October 13, 2016

Name of Division Director signing form: Eric Bastings
Title: Deputy Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

EMILIOS A PAPANASTASIOU
10/21/2016
Tracked Changes Removed

ERIC P BASTINGS
10/24/2016

From: Wendy Tian
To: Papanastasiou, Emilios
Cc: Bullock, Heather
Subject: Re: Clarification for PI/SPL submission - NDA approval Action letter.206030)
Date: Thursday, October 13, 2016 5:37:28 PM

Thank you, will do.

Wendy

Sent from my iPhone

On Oct 13, 2016, at 10:06 AM, Papanastasiou, Emilios <Emilios.Papanastasiou@fda.hhs.gov> wrote:

> Hi Wendy,
>
> Sorry for the late reply. We have received your final printed carton and container labels. Yes, please submit the SPL and final PI. Please see the following for more information:
>
> <!--[if !supportLists]-->● <!--[endif]-->The content of labeling [21 CFR 314.50(l)] should be submitted no later than 14 days after receipt of the action letter (October 21, 2016) in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default htm.
> Content of labeling must be identical to the labeling (text for the package insert) enclosed in the action letter.
>
> Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf .
>
> Please feel free to contact me if you have any questions,
>
> Andrew
>
> ---
>
> **From:** Wendy Tian [mailto:WETI@lundbeck.com]
> **Sent:** Tuesday, October 11, 2016 4:06 PM
> **To:** Papanastasiou, Emilios
> **Cc:** Bullock, Heather
> **Subject:** Clarification for PI/SPL submission - NDA approval Action letter.206030)
>
> Hi Andrew,
>
> As we are preparing to submit the final printed carton and container labels per the approval letter requirement, I am wondering whether we should also submit the SPL and the final printed PI as well. Please advise.
>
> Thank you,
>
> Wendy
>
> ---
>
> **From:** Wendy Tian [mailto:WETI@lundbeck.com]
> **Sent:** Friday, October 07, 2016 4:55 PM
> **To:** Papanastasiou, Emilios
> **Cc:** Bullock, Heather
> **Subject:** RE: NDA Action letter for Carnexiv (NDA 206030)
>
> Hi Andrew and Heather,
>
> This is to acknowledge the receipt of the approval letter. We are thrilled to receive it. We greatly appreciate the advice, review, support, and clear communication from the Agency in NDA application journey.

Best Regards,

Wendy

Wendy Tian
Sr Dir, Regulatory Strategy
Regulatory ICR

Lundbeck LLC
6 Parkway North
Deerfield, IL 60015
United States

www.lundbeck.com

<image001.png>

From: Papanastasiou, Emilios [mailto:Emilios.Papanastasiou@fda.hhs.gov]
Sent: Friday, October 07, 2016 3:41 PM
To: Wendy Tian
Cc: Bullock, Heather
Subject: NDA Action letter for Carnexiv (NDA 206030)
Importance: High

Hi Wendy,

Attached please find the approval letter for Carnexiv (NDA 206030). Please confirm receipt of this message.

Thanks,

Andrew

E. Andrew Papanastasiou, PharmD, MS
Regulatory Health Project Manager

Center for Drug Evaluation and Research
Division of Neurology Products
U.S. Food and Drug Administration

emilios.papanastasiou@fda.hhs.gov

<image002.png>

<image003.jpg> <image004.jpg> <image005.jpg> <image006.jpg> <image007.jpg>

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

/s/

EMILIOS A PAPANASTASIOU
10/14/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206030	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: CARNEXIV Established/Proper Name: carbamazepine Dosage Form: injection		Applicant: Lundbeck, LLC Agent for Applicant (if applicable): N/A
RPM: Heather Bullock and Emilios Papanastasiou		Division: Neurology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is October 8, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ CR 10/23/15
❖ 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 _____	☒ N/A
❖ 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): N/A
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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)*	N/A
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	No
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified

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)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP 10/xxx/16 CR 10/23/2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ N/A
• Original applicant-proposed labeling	☒ N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name: • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	CARNEXIV: conditionally acceptable 07/18/16; the review is dated 05/17/16. CARBELLA: conditionally acceptable 02/5/14; the review is dated 01/30/14.
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 03/04/14 DMEPA: ☒ 09/12/16; 06/28/16; 06/05/14 DMPP/PLT (DRISK): ☒ None OPDP: ☒ 7/26/16 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	03/18/14 ☒ AP: 08/02/16; CR 09/03/14
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ ~~Completed~~ N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan designation granted on June 27, 2013	Orphan designation *for treatment of epilepsy patients who cannot take anything by mouth (NPO)*
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	N/A
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	N/A
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ 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.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Resubmission Ack: 04/21/16 Filing Review Issues: 03/07/14 NDA Ack: 01/08/14
❖ 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)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ no mtg
• Pre-NDA meeting *(indicate date of mtg)*	☒ 09/10/13
• EOP2 meeting *(indicate date of mtg)*	☒ 07/07/09
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	PIND 11/30/05 (IND 73686)
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ ~~TBD~~ 10/07/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ ~~TBD~~ 10/07/2016
PMR/PMC Development Templates *(indicate total number)*	☒ 0

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ 10/23/14
• Clinical review(s) *(indicate date for each review)*	Filing: 02/21/14; Primary 10/15/14: Resubmission 09/29/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Primary review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ 03/25/14
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	N/A
Clinical Microbiology Review(s) *(indicate date for each review)*	N/A
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	N/A
Statistical Team Leader Review(s) *(indicate date for each review)*	N/A
Statistical Review(s) *(indicate date for each review)*	N/A
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ Filing: 06/25/2014; Primary 10/16/2014; None for resubmission
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ Memo dated 10/10/14; 10/23/14
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 9/22/14; None for resubmission
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ N/A
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ Filing: 01/16/14 Primary: 08/23/14; Amended Primary: 10/10/14; Resubmission: 8/29/16; 08/11/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ Microbiology (sterility & pyrogenicity) Filing: 01/16/14 Primary Review: 08/26/14 Resubmission: None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Adequate per CMC Primary Review: 10/14/14 Adequate per CMC Resubmission Review: 08/11/16
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable: Primary Review: 2/17/2014 Resubmission: 06/08/16 ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

Bullock, Heather

From: Holovac, Mary Ann
Sent: Tuesday, August 02, 2016 1:03 PM
To: Bullock, Heather
Cc: Locicero, Colleen L; Goldstein, Beth A (Duvall); Holovac, Mary Ann
Subject: NDA 206030 carbamazepine injection- cleared for acction (again)

Follow Up Flag: Follow up
Flag Status: Flagged

Heather,

We discussed this application (again) at Monday's 505(b)(2) clearance meeting. This application is cleared for action (again) from a 505(b)(2) perspective.

Please make the changes to the draft assessment (if not already done) as outlined in the clearance email from 9/3/14 attached below before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue.

Please let me know if you have any questions.

Mary Ann

From: Holovac, Mary Ann
Sent: Wednesday, September 03, 2014 10:21 AM
To: Bullock, Heather
Cc: Locicero, Colleen L; Bertha, Amy; Duvall, Beth A; Holovac, Mary Ann
Subject: NDA 206030 carbamazepine injection- cleared for acction

Heather,

We discussed this application at Monday's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

Please make the following change to the draft assessment before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue. Great job on the assessment!

- *Q11: Please also include the following applications as pharmaceutical alternatives:* [redacted] (b) (4)

Please let me know if you have any questions.

Mary Ann

From: Bullock, Heather
Sent: Tuesday, September 02, 2014 11:55 AM
To: Holovac, Mary Ann
Cc: Men, Angela; Daugherty, Susan B (CSO)
Subject: RE: 505(b)(2) assessment for NDA 206030 carbamazepine injection

Hi Mary Ann,

Our Clin Pharm reviewer stated, "we believe that the literature reference to the boceprivir DDI is not necessary for approval of the application."

Thank you,
Heather

From: Holovac, Mary Ann
Sent: Tuesday, August 26, 2014 3:27 PM
To: Bullock, Heather
Cc: Holovac, Mary Ann
Subject: RE: 505(b)(2) assessment for NDA 206030 carbamazepine injection

Hi Heather,

I am reviewing the subject application prior to presentation to the 505(b)(2) committee and I have a question I hope you can assist with.

Please see the attached annotated labeling for this application. There is a reference in the labeling on pages 7 and 29 citing a new contraindication/drug interaction with boceprevir that was found in the literature.
Can the division confirm whether or not the application is relying upon this literature? Please note that when literature fills a gap in or is otherwise necessary for approval of the application, the literature is considered relied upon.
If the application is relying upon this literature, does the published literature cite a listed/brand name drug product?

Thank you.
Mary Ann

From: Bullock, Heather
Sent: Friday, August 22, 2014 1:28 PM
To: Holovac, Mary Ann
Cc: Daugherty, Susan B (CSO); Men, Angela
Subject: 505(b)(2) assessment for NDA 206030 carbamazepine injection

Hi Mary Ann,

Attached is our 505b2 assessment.

Thank you,
Heather

From: Bullock, Heather
Sent: Wednesday, August 13, 2014 12:00 PM
To: Holovac, Mary Ann
Cc: Daugherty, Susan B (CSO)
Subject: RE: 505(b)(2) applications at the top of the queue

Hi Mary Ann,

1. Yes we are still on track to take an action on PDUFA date
2. Not 100% sure, clinical and clin pharm are still discussing some issues but I don't think it will be CR
3. 505b2 assessment is almost complete, just waiting to hear from team (by COB on Monday, Aug 18) on a couple of questions. So the assessment will probably be sent next week.

Have a good leave,
Heather

From: Holovac, Mary Ann
Sent: Wednesday, August 13, 2014 11:20 AM
To: Robertson, Kim; Davis, Anissa; Fortney, Russell; Bullock, Heather
Subject: 505(b)(2) applications at the top of the queue

Hello Kim/Anissa/Russell/Heather,

Please see the table below which lists the 505(b)(2) applications and the PDUFA dates that are near the top of the clearance queue. Although we are just outside of the 60 day time frame where I are looking for the 505(b)(2) assessment I just wanted to give you a heads up and touch base to see if you are still on track for an action on the dates listed below. At your convenience, can you please let me know

1. If you are still on track to take an action on the PDUFA date listed below
2. What is the planned action
3. Status of the 505(b)(2) assessment

I will be on leave next week but will plan to work on these applications the following week upon my return if you can send me the assessments on or before 8/25/14.
Thank you!
Mary Ann

(b) (4)

[redacted]

Mary Ann Holovac, R.Ph.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs/Immediate Office
Regulatory Affairs Team
301-796-0136 (office)

301-796-9858 (fax)
MaryAnn.Holovac@fda.hhs.gov
WO Building 22, Room 6478

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206030

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Lundbeck LLC
4 Parkway North
Deerfield, IL 60015

ATTENTION: Wendy Tian
Senior Director, U.S. Regulatory Affairs

Dear Ms. Tian:

Please refer to your New Drug Application (NDA), Class 2, Resubmission dated December 20, 2013, received December 23, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Carnexiv (Carbamazepine), Injection, 200 mg/20 mL.

We also refer to your correspondence, dated and received April 21, 2016, requesting review of your proposed proprietary name, Carnexiv.

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

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ruth Maduro, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4232. For any other information regarding this application, contact Heather Bullock, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
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

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

/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
07/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206030

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Lundbeck LLC
Attention: Wendy Tian
Director US Regulatory Affairs
4 Parkway North
Deerfield, IL 60015

Dear Ms. Tian:

We acknowledge receipt on April 8, 2016, of the resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CARNEXIV (carbamazepine) injection.

We consider this a complete, class 2 response to our October 23, 2014 action letter. Therefore, the user fee goal date is October 8, 2016.

If you have any questions, contact me via email at heather.bullock@fda.hhs.gov, or by telephone at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Heather M. Bullock, RN, BSN, MSHS
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/

HEATHER M BULLOCK
04/21/2016

Bullock, Heather

From: Holovac, Mary Ann
Sent: Wednesday, September 03, 2014 10:21 AM
To: Bullock, Heather
Cc: Locicero, Colleen L; Bertha, Amy; Duvall, Beth A; Holovac, Mary Ann
Subject: NDA 206030 carbamazepine injection- cleared for acction

Follow Up Flag: Follow up
Flag Status: Flagged

Heather,

We discussed this application at Monday's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

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- *Q11: Please also include the following applications as pharmaceutical alternatives:* [redacted] (b) (4)

Please let me know if you have any questions.

Mary Ann

From: Bullock, Heather
Sent: Tuesday, September 02, 2014 11:55 AM
To: Holovac, Mary Ann
Cc: Men, Angela; Daugherty, Susan B (CSO)
Subject: RE: 505(b)(2) assessment for NDA 206030 carbamazepine injection

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To: Bullock, Heather
Cc: Holovac, Mary Ann
Subject: RE: 505(b)(2) assessment for NDA 206030 carbamazepine injection

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From: Bullock, Heather
Sent: Friday, August 22, 2014 1:28 PM
To: Holovac, Mary Ann
Cc: Daugherty, Susan B (CSO); Men, Angela
Subject: 505(b)(2) assessment for NDA 206030 carbamazepine injection

Hi Mary Ann,

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Thank you,
Heather

From: Bullock, Heather
Sent: Wednesday, August 13, 2014 12:00 PM
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Cc: Daugherty, Susan B (CSO)
Subject: RE: 505(b)(2) applications at the top of the queue

Hi Mary Ann,

1. Yes we are still on track to take an action on PDUFA date
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Heather

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Sent: Wednesday, August 13, 2014 11:20 AM
To: Robertson, Kim; Davis, Anissa; Fortney, Russell; Bullock, Heather
Subject: 505(b)(2) applications at the top of the queue

Hello Kim/Anissa/Russell/Heather,

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Thank you!
Mary Ann

(b) (4)

Mary Ann Holovac, R.Ph.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs/Immediate Office
Regulatory Affairs Team
301-796-0136 (office)
301-796-9858 (fax)
MaryAnn.Holovac@fda.hhs.gov
WO Building 22, Room 6478

From:	Bullock, Heather
To:	"Wendy Tian"
Cc:	Daugherty, Susan B (CSO)
Subject:	NDA 206030 - Container and Carton comments
Date:	Monday, June 16, 2014 12:16:00 PM

Hi Wendy,

We have the following container and carton comments:

1. Container Label
    a. Revise the statement [redacted] (b) (4) to minimize the risk of administering the drug as a bolus injection.

2. Carton Labeling
    a. See Section 1.a.
    b. Debold the statement [redacted] (b) (4) under the usual dosage heading on the side panel as it makes the statement overly prominent

Thank you,
Heather

Heather Bullock, RN, BSN, MSHS
Lieutenant Commander, United States Public Health Service
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA

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

/s/

HEATHER M BULLOCK
06/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206030

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Lundbeck LLC
Attention: Wendy Tian
Director, US Regulatory Affairs
4 Parkway North
Deerfield, IL 60015

Dear Ms. Tian:

Please refer to your New Drug Application (NDA) dated December 20, 2013, received December 23, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for CARBELLA (carbamazepine) injection 200 mg/20 mL.

We also refer to your amendments dated January 13, 2014, January 16, 2014, and January 30, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 23, 2014.

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 25, 2014.

We request that you submit the following information:

Chemistry, Manufacturing, and Controls

1) Submit a comprehensive regulatory acceptance specification for carbamazepine (i.e., test parameters, analytical procedures, and acceptance criteria) to the NDA. The specification should include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt or periodically for vendor requalification. You may incorporate USP compendial methods by reference. Provide all other analytical procedures and supporting method validation data in the application.

2) You propose intravenous administration of 70% of the corresponding oral carbamazepine dose. As this is a new route of administration, provide justification for any drug substance impurity that exceeds the ICH Q3A qualification threshold (b) (4)%) corresponding to a maximum daily dose equal to 1120 mg (70% of 1600 mg).

3) Provide data regarding the solubility of carbamazepine in aqueous betadex sulfobutyl ether sodium solution at reduced temperature (e.g., (b) (4)). Additionally, provide refrigeration to (b) (4) temperature cycling results for at least one stability batch.

4) Provide data to support the physical and chemical compatibility of the product with manufacturing equipment, (b) (4).

5) Provide data to support the physical and chemical compatibility of the product with the labeled diluents, infusion bags and IV tubing.

6) Revise the process description [Module 3.2.P.3.3] to include labeling and packaging procedures. Provide master batch production records for labeling and packaging.

7) The proposed acceptance limits of not more than (b) (4)% at release and (b) (4)% on stability for (b) (4) in the drug product exceed the ICH Q3B qualification threshold (0.2%) corresponding to a maximum daily dose equal to 1120 mg (70% of 1600 mg). Revise the release and shelf-life limits for consistency with ICH or provide data to support the proposed limits.

8) Revise the stability protocols for commercial scale batches to include long-term storage testing in inverted orientation.

Clinical Pharmacology

1. Definition Files: Please provide a definition file for each of the following files:

    - cbz-auc-70-75-80.xls
    - cbzindparadose.xls
    - cbzpartial-aucsq4.xls
    - cbzsimconcq4.xls

    In each definition file, please include variable descriptions and, where applicable, units of measurement. In addition, please clarify the location of the simulated data representing the 75% and 80% oral dose conversion within the cbz-auc-70-75-80.xls file (only simulated data representing the 70% oral dose conversion data could be found). If the simulated data representing the 75% or 80% oral dose conversion were not included in the NDA submission, please submit them. Also, file cbzsimconcq4.xls appears to contain simulated concentrations for a single q4h IV infusion. Please re-submit cbzsimconcq4.xls with simulated concentrations for the full week of treatment (Day 1 to Day 7) for each subject using the corresponding q4h IV infusion regimen.

    In addition, please include any relevant PK simulation parameters in the adpc.xpt dataset for study ov-1015-pauc (e.g., oral-to-IV dose conversion value, IV infusion interval [e.g., q4hr, q6hr], etc.]) and resubmit this dataset.

2. Project Files: Please submit Pharsight Phoenix project files (e.g., *.phxproj), input datasets, output datasets (e.g., individual simulated PK values) and any other files that are relevant to the IV infusion simulations. Also, please provide any scripts, spreadsheets, or other files relevant to the computation of any AUC values (for example, the partial AUC values) derived from the aforementioned simulated IV PK data.

3. New Simulations: The PK simulation results shown in Figure 6 on page 13 in the *OV-1015-MODSIM* report demonstrate that the partial AUC 90% CI is expected to fall outside of the 80-125% range at various time points when switching to IV from oral IR q8hr carbamazepine. We recommend you conduct PK simulations to explore the feasibility of utilizing different dosing regimens and/or infusion parameters with a goal of producing an IV infusion concentration profile that meeting bioequivalence based on partial AUC after oral IR q8h carbamazepine and oral ER q12h carbamazepine. We also recommend assessing the bioequivalence of C_{max} and C_{min} for this alternative IV infusion regimen in comparison with oral IR q8h carbamazepine as well as oral ER q12h carbamazepine.

    It is possible the simulated PK data for the alternate IV infusion regimen may not achieve bioequivalence at every time point for the aforementioned exposure metrics for oral IR q8h and/or oral ER q12h carbamazepine. If so, and if you do not expect

the alternate IV infusion regimen to result in a clinically significant worsening of efficacy or safety, please provide your justification.

Clinical

There appears to be an irregularity of financial disclosures provided in form 3454 for study (b) (4). Only one investigator, the Principal investigator, is listed for each study site. The Guidance for Clinical Investigators, Industry and FDA staff , Financial Disclosure by Clinical Investigators (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf) indicates the definition of "Clinical Investigator" to include *"listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects."* Therefore subinvestigators should be included in the financial disclosure certification. Please provide financial disclosure certification for all personnel at each study site who meet the definition of "clinical investigator" as defined in the guidance.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Avoid using vague, misleading terms such as "potent," "generally," and "small children".

2. Avoid arbitrary categories of "mild," "moderate," and "severe" that do not have established definitions.

3. Define "BUN" abbreviation at first use.

4. Use command language throughout the document (e.g., "Discontinue" instead of "Should discontinue").

5. Throughout the document, spell out "greater than" or "less than" rather than using the symbols.

6. Throughout the document, use commas for dosing units at or above 1,000 to improve readability.

7. To avoid confusion, do not abbreviate drug names. We suggest spelling out the abbreviation "CBZ" throughout the document.

8. Define all abbreviations in all the tables.

9. In Table 2, define the abbreviation "AED".

10. Under Highlights (HL), Product Title: use lowercase “i” for “Injection”.

11. Under HL, horizontal line for INDICATIONS AND USAGE and WARNINGS AND PRECUATIONS does not extend over entire width of the column.

12. Under HL, WARNINGS AND PRECAUTIONS Section 5.8, the condition referenced does not use the same terminology as in the Full Prescribing Information (FPI).

13. Under FPI, *4 Contraindications*: because there is more than one contraindication, use an introductory statement followed by the bulleted list (e.g., “CARBELLA is contraindicated in:”)

14. Under FPI, *5 Warnings and Precautions,*
    a. *5.5 Embryofetal Toxicity*: per 21 CFR 201.57(c)(9)(i), the brief description of human data and any animal data is missing from the following statement….‘‘CARBELLA can cause fetal harm when administered to a pregnant woman. [*Briefly describe the human data and any pertinent animal data*]. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, (b) (4) the patient of the potential hazard to a fetus.’’

15. Under FPI, Section 6.2, first sentence, please add a hyphen between post” and “approval".

16. Under FPI, *8 Use in Specific Populations,*
    a. Subsection *8.1 Pregnancy*: use subheadings “*Teratogenic Effects*” and “*Nonteratogenic Effects*” followed by “*Pregnancy Registry*”
    b. The pregnancy category information should be included under “*Teratogenic Effects*”
    c. Subsection 8.6 and table of contents: change heading to “*Renal Impairment*”.

17. Under FPI, *10 Overdosage,*
    a. Describe concentrations of drug in biologic fluids associated with toxicity or death.

18. Under FPI, *16 How Supplied/Storage and Handling*
    a. Use the statement “Not made with natural rubber latex” if the product does not contain latex and the manufacturing of the product and container did not include the use of natural rubber latex or synthetic derivatives of natural rubber latex. May include a statement that certain components of the product are not made with latex, such as “the vial cap is not made with natural rubber latex.”

We request that you resubmit labeling that addresses these issues by March 28, 2014. The resubmitted labeling will be used for further labeling discussions.

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). 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 you 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.

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.

Your application is exempt from the requirements of PREA because orphan designation has been assigned for the requested indication.

If you have any questions, 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

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
03/07/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206030

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Lundbeck LLC
4 Parkway North
Deerfield, IL 60015

ATTENTION: Wendy Tian
Director, US Regulatory Affairs

Dear Ms. Tian:

Please refer to your New Drug Application (NDA) dated December 20, 2013, received December 23, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Injection, 200 mg per 20 ml (10 mg/ml)..

We also refer to your correspondence dated and received January 16, 2014, requesting review of your proposed proprietary name, Carbella. We have completed our review of the proposed proprietary name, Carbella, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 16, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Heather Bullock, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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 on behalf of KELLIE A TAYLOR
02/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206030

NDA ACKNOWLEDGMENT

Lundbeck LLC
Attention: Wendy Tian
Director, US Regulatory Affairs
4 Parkway North
Deerfield, IL 60015

Dear Ms. Tian:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: carbamazepine injection

Date of Application: December 20, 2013

Date of Receipt: December 23, 2013

Our Reference Number: NDA 206030

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 February 21, 2014, 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).

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 via email at heather.bullock@fda.hhs.gov or via telephone at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Heather M. Bullock, RN, BSN, MSHS
Lieutenant Commander,
United States Public Health Service
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/

HEATHER M BULLOCK
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073686

MEETING MINUTES

Lundbeck LLC
Attention: Wendy Tian
Director, Regulatory Development & Registration
Four Parkway North
Deerfield, IL 60015

Dear Ms. Tian:

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

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2013. The purpose of the meeting was to discuss Lundbeck's proposed NDA application submission plan.

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, call Su-Lin Sun, PharmD, Regulatory Project Manager, at (301) 796-0036 or email su-lin.sun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, 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: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 10, 2013 3:00PM to 4:00 PM (EST)
Meeting Location: FDA, White Oak Campus, Building 22, Room 1311

Application Number: IND 073686
Product Name: Carbamazepine injection
Indication: Partial seizures with complex symptomatology (b) (4)

- Generalized tonic-clonic seizures (b) (4)
- Mixed seizure patterns which include the above, or other partial or generalized seizures. (b) (4)

Sponsor/Applicant Name: Lundbeck LLC

Meeting Chair: Eric Bastings, MD, Acting Director
Meeting Recorder: Su-Lin Sun, PharmD

Eric Bastings, MD, Acting Division Director
Billy Dunn, MD, Acting Deputy Director
Norman Hershkowitz, MD, Clinical Team Leader
Steven Dinsmore, DO, Medical Officer
Martha Heimann, Chemistry, Manufacturing, and Controls Lead
Charles Jewell, PhD., Chemistry, Manufacturing, and Controls Reviewer
Angela Men, PhD, MD, Clinical Pharmacology Team Leader
Michael Bewernitz, PhD, Clinical Pharmacology Reviewer
Su-Lin Sun, PharmD, Sr. Regulatory Project Manager
Margaret Lim, PharmD, Pharmacy Student

Office of Surveillance & Epidemiology (OSE)
George Neyarapally, PharmD, MPH, Drug Risk Management Analyst (DRISK, OSE)
Julie Villanueva Neshiewat, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)

SPONSOR ATTENDEES (Lundbeck LLC):

Program Management:
Anders Buur, PhD, Vice President, US Drug Development
Suresh Dheerendra, MS, Sr. Clinical Project Manager

Clinical and Medical:
Chris Silber, MD, Vice President
Deborah Lee, MD, PhD, Sr. Medical Director

Clinical Pharmacology/Pharmacometrics:
Dwain Tolbert, PhD, FCP, Executive Director
Aziz Karim, PhD, FCP, ABCP, Consultant

Nonclinical Toxicology:
Tomas Mow, DVM, PhD, Head of Department

US Pharmacovigilance:
Uwa Kalu, MD, Sr. Medical Director

Biostatistics:
Guangbin Peng, MS, Principal Statistician

Pharmaceutical Development (Chemistry, Manufacturing, and Controls):
Kirstine Høeg-Møller, MS, Section Lead
Aravind Krishna, PhD, Consultant

Regulatory Affairs:
Eric Floyd, PhD, Vice President, US Regulatory Affairs
Lois Householder, Associate Director, US Regulatory Affairs
Wendy Tian, MS, Director, Regulatory Strategy
Jane Stachura, MS, Vice President, Chemistry, Manufacturing, and Controls Regulatory

1.0 BACKGROUND

This meeting is to discuss Lundbeck's proposed plan for developing an IV formulations of carbamazepine as replacement therapy for patients unable to take their oral carbamazepine due to illness, surgery, or a change in mental status.

Carbamazepine injection is a sterile, IV solution for infusion containing 10mg/mL carbamazepine and 250mg/mL betadex sulfobutyl ether sodium in water for injection.

The Division and Lundbeck had an End-of-phase 2 meeting on July 7, 2009. Advice at the meeting and actions taken are summarized in Table 1.

Orphan Drug Designation Request granted by FDA in June 2013.

Table 1 FDA's Advice at End-of-Phase 2 Meeting and Actions Taken by Lundbeck

FDA's advise at End-of-phase 2 meeting	Lundbeck's Actions
When reporting the assessment of the relative bioavailability of IV to oral carbamazepine, submit individual, mean, and 90% confidence interval data on parent carbamazepine, carbamazepine 10,11-epoxide, and the summation of carbamazepine with carbamazepine 10, 11-epoxide concentrations.	Requested analyses will be provided with NDA submission.
The PK data for each cohort in Study OV-1015 should be evaluated individually as the infusion rates are different and this may lead to differences in the C_{max}.	Requested analyses will be provided with NDA submission.
The relative bioequivalence of carbamazepine injection compared to oral carbamazepine will be assessed at steady state only, although PK data following the first IV dose should also be submitted.	Requested analyses will be provided with NDA submission.
Assessments for all infusion durations (15 minutes, 30 minutes, and open line), and examination of dosage subgroups within each infusion duration strata should be submitted.	Requested analyses will be provided with NDA submission.
An efficacy study and a thorough QT study are not necessary.	No action necessary.
The safety database should include approximately 200 patients exposed to carbamazepine injection with approximately 40% of patients receiving higher infusion rates and dosages than proposed in labeling.	See Section 6.1.1. (of the meeting package)
Enrollment of patients with moderate-to-severe renal impairment should be considered, using lower carbamazepine injection doses (thus lower SBECD exposures).	See Section 6.1.2. (of the meeting package)
Additional information on the safety of SBECD should be provided at expected exposures from available human and animal literature, post marketing safety data and any other relevant data source concerning safety / toxicity of SBECD, particularly in the range of 35,000 mg/day.	See Section 6.1.3. Detailed supporting study data and scientific rationale will be provided with NDA submission.
There was no objection to the choice of rat as the species selected for the embryo-fetal development study.	Study has been completed. The study report will be provided with the NDA submission.

Abbreviations: C_{max} = maximum observed concentration; IV = intravenous; NDA = new drug application; PK = pharmacokinetic(s); SBECD = sulfobutylether beta-cyclodextrin sodium salt.

2. DISCUSSION

I. CLINICAL AND CLINICAL PHARMACOLOGY

Question 1:
Does the Agency agree that the number of patients exposed to higher doses and higher infusion rates is sufficient to support the NDA filing?

Preliminary FDA Response:

Yes.

Meeting Discussion: None

Question 2:
Does the Agency agree that sufficient information is available to provide appropriate labeling recommendations for patients with renal impairment?

Preliminary FDA Response:

Ultimately, the acceptability of the proposed labeling statements based on the provided data will be a review issue. While there may be sufficient numbers of patients with minimal renal impairment, there are only 2 patients with moderate renal impairment. It is unlikely that 2 patients will adequately represent patients with this degree of renal impairment. In addition, no patients with severe hepatic impairment were enrolled, as the Agency had requested during the EOP2 meeting.

FDA's Clarification Comment (09-10-13)

The last sentence on the above comments should be "In addition, no patients with severe renal impairment were enrolled, as the Agency had requested during the EOP2 meeting."

Meeting Discussion: None

Question 3:
Does the Agency agree that the scientific rationale for the safety of SBECD (Captisol®) exposure in carbamazepine injection, as summarized in the briefing document, is sufficient to support the NDA filing?

Preliminary FDA Response:

On face the information appears sufficient; however see response to question 6 concerning reference to non-Lundbeck sources

Meeting Discussion: None

II. STATISTICAL

Question 4:
Does the Agency agree with the proposed data displays and analyses outlined in the statistical analysis plan (SAP) to integrate the safety results from Studies OV-1015 and 13181A?

Preliminary FDA Response:

See response to Q 7 concerning proposed data presentation plan.

Meeting Discussion: None

III. Chemistry, Manufacturing, and Controls

Question 5:
Does the Agency agree that the content of the Chemistry, Manufacturing, Controls portion of the application, as described in the briefing document, is sufficient to support the NDA filing and review?

Preliminary FDA Response:

Your provided outline of chemistry, manufacturing and controls information appears adequate for submission; however we advise the following to facilitate the review process:

- Provide the full actual or proposed manufacturing details of packaged/sterilized drug product in section 3.2.P.3.3 Description of Manufacturing Process and Process Controls. This should include details of the equipment used in the process. This application also requires an actual or proposed batch production record including description of equipment. (see 21 CFR 314.54 (a)(1)(i))
- Provide batch analysis data for all drug substance lots used in the manufacture of the drug product batches used for registration stability ((b) (4) sourced) and compare to the Teva drug substance batches being used in the continuing commercial process development. In addition, provide representative batch analysis data from drug substance batches used in key drug product development studies.
- Provide an explanation for the choice of concentrations tested for in-use studies based on concentrations to be used in practice.

Meeting Discussion: None

IV. REGULATORY

Question 6:
Does the Agency agree that Carbamazepine Injection can be filed as a 505(b)(2) NDA with Tegretol® (oral carbamazepine immediate release, 400mg (NDA 16-608) as the reference listed product?

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

Please note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX "TRADENAME"	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY "TRADENAME"	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Lundbeck's response (09-10-13)

We revised the original proposal and will propose to use Tegretol IR, 200 mg, NDA16-608 and Tegretol XR, 400 mg, NDA 20-234 as the RLDs. Does the Agency concur this proposal?

FDA's response (09-10-13)

A 505(b)(2) application may rely for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs. The Agency typically does not advise a sponsor on the selection of a particular listed drug or drugs that may be relied upon to support approval of a proposed product. (An exception is that if there is a listed drug that is a pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as a listed drug (as described in the draft *Guidance for Industry: Applications Covered by Section 505(b)(2)* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf).) However, your proposal to rely on Tegretol IR Tablets (NDA 16608) and Tegretol XR Tablets (NDA 20234) appears acceptable at this time, based on the information provided. Please note that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Lundbeck's response (09-10-13)

Following your comments, we will include a list of reference information to identify each section of the 505(b)(2) application and labeling that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. Could the Agency please advise which sections in CTD M1 you want us to place this list of information? We prefer not to include this list in the cover letter due to life cycle maintenance reason, rather we propose to cross reference this list in the cover letter and hyperlink it to the M1 sections.

Meeting Discussion: None

Post Meeting Note (09-11-13):

FDA CDER_ESUB team recommended you to submit a document in section 1.4.4 of the eCTD that lists all specific references.

Question 7:
Does the Agency agree our proposal that the Integrated Safety Summary report does not need to be included in the NDA dossier?

Preliminary FDA Response:

No, we request that a formal integrated summary of safety (ISS) is submitted to module five and all regulatory guidelines for the ISS be followed including hyperlinks to source documents. The narrative ISS may be used as the summary component for module 2 assuming it fulfills formatting criteria for that section.

We are in agreement with your safety data analysis plan reporting by infusion time and dose groups and planned presentation of AEs and shift tables; however, we disagree with your designated cut point of -30 mmhg for abnormal orthostatic systolic blood pressure and recommend a threshold of -20 mmhg for this parameter.

We request that you provide pooled analysis datasets in SAS transport file or .xpt format for studies OV-1015 and 13181A combined. These dataset entries were not seen in your NDA table of contents, section 10.5. These datasets should include demographics, carbamazepine oral regimen and IV dose, adverse events, concomitant AEDs, concomitant medications, ECG, epilepsy history / diagnosis, chemistry, hematology, neurologic examination, physical examination, renal biomarkers, and vital signs. Please add a dose and duration variable to these datasets.

We also request a separate document which bundles narratives for deaths, SAEs, adverse events leading to withdrawal and discontinuations, into a single PDF document. This document should have a title page for each of these categories which links to the line listing of each category and each event in the line listing links to the case narrative, all contained within the same document.

Lundbeck's response (09-09-13)

1. We have extracted the CRFs data including all the information requested into the datasets following SDTMs standard for two studies separately. In accordance with integrated safety analysis plan (SAP), we have created 6 integrated datasets following ADaMs standard to generate integrated analyses. These datasets are ADSL, ADAE, ADCM, ADDS, ADVS, ADLB including demographics, dose information, exposure (duration and infusions), adverse events, concomitant AEDs and non-AEDs, patient's disposition, vital signs and lab measurements (chemistry, hematology). Do you need analysis programs submitted with the datasets?

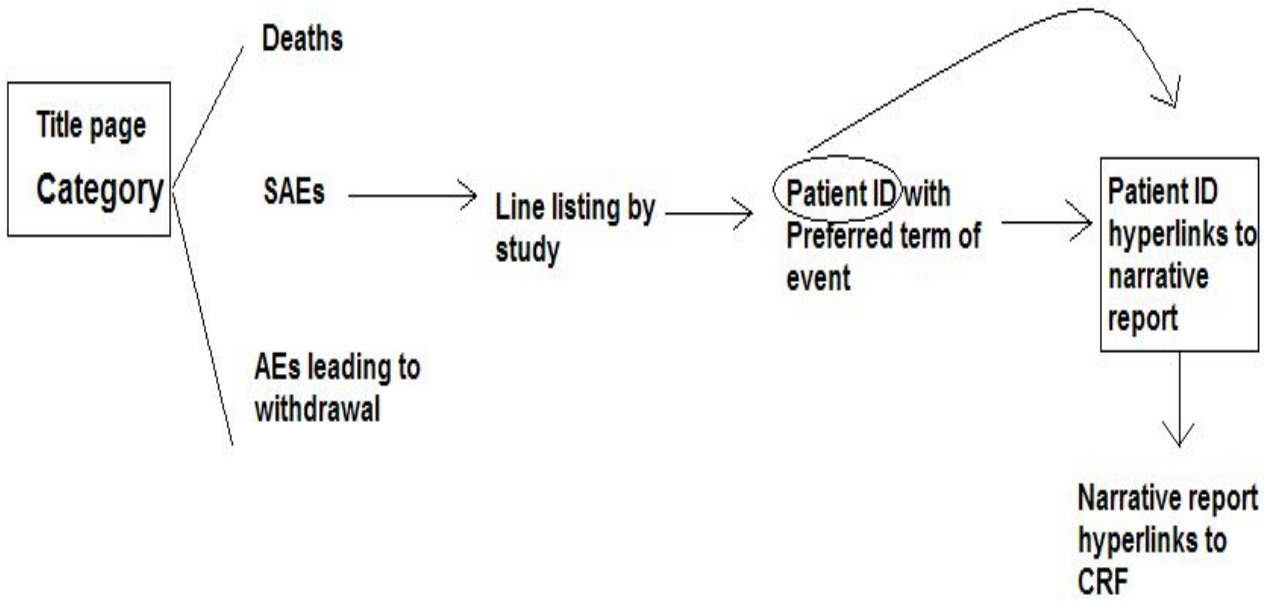
We plan to submit only SDTM datasets by each study for the following parameters: ECG, epilepsy history, neurological examination, physical examination. Is this acceptable?

We also want to clarify for the Agency that the renal biomarkers assay results for the two studies were generated by different central labs. We propose to analyze the data separately for each study due to different analytical conditions

2. We saw the comment that the Agency requests a separate document which bundles narratives for deaths, SAEs, adverse events leading to withdrawal and discontinuations, into a single PDF document. We are unclear why a separate document is requested. We propose to provide this information as appendices to the ISS with all appropriate hyperlinks. Is this acceptable?

FDA's comment:

You may include this information as an ISS appendix but we request structure as shown in the attached flow graphic. The purpose is for ease of identifying each grouping of events then easily navigating from line listing (with PT for event) to the full narrative report. We also request the narrative report link to the CRF. This is show schematically in the figure below with SAEs showing the desired flow of hyperlinks



Meeting Discussion:

The Division agreed that the sponsor proposal for dataset content is acceptable.

For presentation of deaths, SAEs, and AEs leading to discontinuation a single searchable document with line listings and narratives is requested. This may be placed in the ISS as an appendix. Hyperlinks from this document to the CRFs are also requested.

Question 8:
Does the Agency agree with Lundbeck proposed strategy as outlined in the briefing document for populating each section of the Carbamazepine Injection labeling?

Preliminary FDA Response:

Yes. All information must ultimately be referable to the Tegretol label. Also see our answer to question 6. You should also obtain current drug-drug interaction information from published literature.

Meeting Discussion: None

Question 9: Does the Agency agree that Medication Guide and Risk Evaluation and Mitigation Strategy (REMS) is not required for the proposed IV drug product?

Does Agency agree that Medication Guide or Risk Evaluation and Mitigation Strategy (REMS) is not required for the proposed IV drug product?

Preliminary FDA Response:

A medication guide for an intravenous AED is not usually required. Whether a REMS will be needed for any yet to be identified safety concern will be a review issue.

Meeting Discussion: None

Question 10:
Lundbeck is requesting priority review designation for Carbamazepine Injection NDA application. Does the Agency agree with this proposal?

Preliminary FDA Response:

Review designation will be made at the time of NDA submission.

Meeting Discussion: None

3.0 Other Comments

The maintenance dosing schedule for Tegretol IR is either q8h or a6h and for Tegretol XR is q12h. The shape of the PK profile is an important factor in AED safety and efficacy. Your BE analyses appear to compare PK after switching to intravenous CBZ at a dosing schedule of q6h

to PK from patients treated with all of these potential oral CBZ dosing schedules. It is likely that the bioequivalence can extrapolated from oral q6h to intravenous q6h. However, we are uncertain as to how safety and efficacy equivalence can be extrapolated from oral q12h or q8h dosing to intravenous q6h hours dosing as the shape of the PK profiles would be different. This should be discussed.

Lundbeck's response (09-09-13)

Please note that prior to administration of intravenous carbamazepine q6h, we have 73 patients out of 98 receiving oral dose CBZ at q12h, 24 patients out of 98 receiving oral dose CBZ at q8h, and 1 patient receiving oral dose at q6h in the bioavailability study (OV-1015). All dosing regiments were normalized to a 24 hours total daily systemic exposure prior to BE analysis.

Meeting Discussion:

Based upon a review of Lundbeck's pre-meeting response, the Division learned that data exists on only one patient transitioning from a q.i.d. oral dose regimen to the q6h intravenous schedule. (b) (4) **The Division reiterated that the shape of the concentration-time curve may markedly differ between oral and intravenous treatment in those patients on b.i.d. or t.i.d. oral dose** (b) (4) **. This difference may affect the safety and efficacy of the product. The Division emphasized that formal bioequivalence standards should be met for the introduction of a new formulation..**

Because of the difference in dosing schedules that the Sponsor is recommending (e.g., (b) (4) **to q6h), the Division advised the Sponsor to examine the approach used for the approval of Trokendi, which compared XR and IR formulations. This approach utilized short interval sequential concentrations and partial AUCs. The Sponsor expressed a concern that when multiple BE comparisons are performed, some of the comparisons may not pass the BE criteria. The Sponsor wished to know how the Agency would interpret such BE results. The Agency suggested that the Sponsor provide a rationale as to why the safety and efficacy profile is not expected to be significantly influenced by the particular time point(s) that do not meet BE.**

The Division also suggested the exploration of a single dose study as an approach to support equivalence between oral tablet and IV formulations. An issue as to how carbamazepine auto-induction would change the results and how this might be explored was raised by FDA.

Another alternative to bridge the PO intake schedule to the IV regimen would be to present a PK-PD argument.

If an additional study were to be conducted, the Agency mentioned that it may be beneficial to consider looking into different combinations of IV dose and infusion rate for each potential oral dosing regimen (q12h, q8h, and q6h). If adjustments to the IV infusion rate and/or dose were to provide a closer approximation of the PK profile of each different oral

dosing regimen (e.g. q12h, q8h, or q6h), then such an approach may be supportive of approval. The Sponsor indicated that they would submit a new PK analysis plan and the Agency confirmed accepted to review such a plan.

FINANCIAL DISCLOSURE

Investigator financial disclosure must be in accord with the February 2013 "Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators"

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.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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 following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

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.

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

None

5.0 ACTION ITEMS

None

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/s/

ERIC P BASTINGS
10/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73,686

MEETING MINUTES

Lundbeck, Inc.
Attention: Byron Scott, Ph.D.
Vice President, Global Regulatory Affairs
Four Parkway North
Deerfield, IL 60015

Dear Mr. Scott:

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

We also refer to the meeting between representatives of your firm and the FDA on July 7, 2009. The purpose of the meeting was to discuss your development program for intravenous carbamazepine as replacement therapy for patients unable to take oral carbamazepine.

A copy of the official minutes of the meeting is attached for your information. Please notify 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:	July 7, 2009
Meeting Type:	Type B
Meeting Category:	EOP2
Meeting Location:	White Oak Bldg #22, Room 1313
Application Number:	IND 73,686
Product Name:	IV carbamazepine/Captisol
Received Briefing Package	May 29, 2009
Sponsor Name:	Lundbeck Inc.
Meeting Requestor:	Byron Scott, R.Ph.
Meeting Chair:	Russell Katz, M.D.
Meeting Recorder:	Susan Daugherty
Meeting Attendees:	

FDA Attendees

Division of Neurology Products (DNP)
Russell Katz, M.D., Director
Steven Dinsmore, M.D., Clinical Reviewer
Lois Freed, Ph.D., Supervisory Pharmacologist
Tsvi Aranoff, M.D., Clinical Reviewer
Susan Daugherty, Regulatory Project Manager

Division of Clinical Pharmacology I
Hristina Dimova, Ph.D., Clinical Pharmacology Reviewer

External Attendees:

Lunbeck, Inc.
Chris Silber, M.D., Vice President, Clinical Affairs
Tim Cunniff, Pharm.D., Vice President, Global Regulatory Affairs
Mark Weinberg, M.D., M.B.A., Vice President, Clinical Research

Bob Anders, Pharm.D., Vice President, Clinical Operations
Byron Scott, R.Ph., Vice President, Regulatory Affairs
Dwain Tolbert, Ph.D., Executive Director, Nonclinical/Clinical Pharmacology
David Wesche, M.D., Ph.D., Senior Medical Director, Clinical Research
Rebecca Drummond, Ph.D., Senior Biostatistician, Clinical Biostatistics
David Baran, B.S., Senior Project Manager, Clinical Operations
Mark Walzer, Ph.D., Senior Scientist, Nonclinical/Clinical Pharmacology
Jane Stachura, Senior Director, Regulatory Affairs, CMC

1.0 BACKGROUND

The Sponsor submitted an end-of-Phase 2 (EOP2) meeting request on April 28, 2009, to discuss their development program for intravenous carbamazepine as replacement therapy for patients unable to take oral carbamazepine for epilepsy.

Responses from the FDA are in bold following each question and the meeting discussion is bolded and italicized.

2.0 DISCUSSION

Question 1:
Does the Division agree that assessing the summation of carbamazepine and carbamazepine-l0, ll-epoxide concentrations (ie., total carbamazepine) is acceptable to support the demonstration of bioequivalence of iv carbamazepine and oral carbamazepine?

Preliminary FDA Response:
Relative BE will be assessed mainly on the parent carbamazepine. But we will also take into consideration the summation of carbamazepine and carbamazepine-10,11-epoxide concentrations and carbamazepine-10,11-epoxide concentrations alone as well for the assessment of relative bioavailability of IV carbamazepine compared to oral carbamazepine. You should submit individual, mean and 90% CI data on all three assessments [CBZ, CBZ+CBZE and CBZE alone].

We will consider comparisons following the first IV dose in our review.
Also, please refer to Clinical Pharmacology comments for the Type C meeting (sent to sponsor Jan 7, 2008): "The sponsor should evaluate PK data for each cohort individually as the infusion rates are different and this may lead to differences in the Cmax." You should also submit a subgroup analysis based on each dosing cohort, although we recognize that this would not be adequately powered.

Also, please refer to the pIND meeting (Nov 30, 2005) recommendation that you gather some safety experience at higher doses/higher infusion rates during development. The open-line infusions results from study OV-1015 are of limited value, as the actual infusion duration ranged from 2 to 26 minutes (target 2 to 5

minutes).

Meeting discussion:
It was clarified that, while the sponsor should submit PK data following the first IV dose, relative BE of IV carbamazepine compared to oral carbamazepine will be assessed at steady state only.

The sponsor clarified that 80% of the patients in the open-line infusion group (total of 13 patients) received infusions ranging from 2 to 5 minutes.

Question 2:
If the Division agrees with Question 1, does the Division also agree that IV carbamazepine infused over 30 minutes would be considered bioequivalent to oral carbamazepine based upon preliminary data presented within this briefing document?

Preliminary FDA Response:
The results of this study will be a review issue and assessment of bioequivalence cannot be made at this time. You should submit your assessment for all infusion durations (15min, 30 min and open line), and examination of dosage subgroups within each infusion duration strata, in the NDA.

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

Question 3:
If the Division agrees with Questions 1 and 2, does the Division also agree that no efficacy study is required for the approval of iv carbamazepine, given that bioequivalence with oral carbamazepine has been demonstrated?

Preliminary FDA Response:
Yes, with regard to efficacy. While an efficacy study is not necessary it is our impression that there may be an insufficient safety data if you depend upon the presently available data (see below).

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

Question 4:
Does the Division agree that the proposed labeling statement "Patients with moderate-to-severe renal impairment (b) (4)." would be appropriate since the OV-IOIS trial did not enroll subjects with moderate-to-severe renal impairment?

Preliminary FDA Response:
Based on the published literature on voriconazole, the clearance of sulfobutylether beta-cyclodextrin sodium salt [SBECD] is decreased in patients with moderate-to-severe renal impairment resulting in substantially higher SBECD exposures in subjects with moderate renal impairment compared to subjects with normal renal function. However, whether any toxicity in these patients was due to the elevated

SBECD levels on the voriconazole is unknown. It is possible that a study can be done safely on patients with renal impairment which would be preferable.

Meeting discussion:
The sponsor should consider enrolling subjects with moderate-to-severe renal impairment using lower IV carbamazepine doses (thus lower SBECD exposures).

Question 5:
Does the Division agree that a thorough QT (TQT) study would not be required for the approval of IV carbamazepine, given the lack of QT concerns at therapeutic doses of oral carbamazepine and the rigorous collection of cardiac safety data from Study OV-1015?

Preliminary FDA Response:
Yes.

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

Question 6:
Does the Division agree that assessment of iv carbamazepine in relevant pediatric populations, pursuant to 21 CFR 314.55, may be deferred until after approval of the adult indication?

Preliminary FDA Response:
This may be an acceptable deferral; however, please note that per FDAAA of 2007, the PeRC must review all decisions regarding PREA waivers, deferrals, and pediatric plans and assessments prior to the Division taking any action.

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

Question 7:
Lundbeck Inc. proposes to submit this 505(b) (2) eCTD with quality, nonclinical, and clinical data (Study OV-1015) that supports IV carbamazepine. Lundbeck Inc. does not plan to include historical data on oral carbamazepine in support of this application. In addition we also propose 3 year Hatch Waxman exclusivity. Does the Division agree with these proposals?

Preliminary FDA Response:
With regard to carbamazepine, yes. As the we have some concern regarding the Captisol component and it appears that the anticipated Captisol exposures in the present product is greater then that in those marketed, additional information should be provided on the safety of this Captisol. Thus, you should provide additional information on the safety of Captisol at expected exposures from available human and animal literature, post marketing safety data and any other relevant data source concerning safety / toxicity of Captisol, particularly in the range of 35,000 mg/day.

A 505(b)(2) application may be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j); 314.108(b)(4) and (5)). The exclusivity determination may not be made until completion of the review.

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

Question 8:
Does the Division agree that the proposed Embryo-Fetal Toxicology draft study protocol (OVNC-9022) in the rat is sufficient to address Nonclinical Item #2 in the minutes from the pre-IND meeting that occurred on 30 November 2005?

Preliminary FDA Response:
The draft study protocol (OVNC-9022) was not provided in the briefing package. The protocol was received in a subsequent submission, but not in sufficient time to provide comments.

Meeting Discussion:
The Division indicated that there was no objection to the choice of rat as the species selected for the embryo-fetal development study.

Question 9:
Does the Division agree with the plan that Lundbeck Inc. will not submit a 4 month Safety Update, since Study OV-IOI5 will not enroll additional subjects?

Preliminary FDA Response:
You will not need to submit a 4-month safety update if all of the safety data from OV-1015 is submitted in the initial NDA package.

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

Additional comments:

1. **Safety data for exposure of at least 200 patients should be provided in the NDA. The safety data should include adequate numbers of patients exposed to rapid infusion rates. Dose and regimen for a majority of patients exposed should reflect, or exceed, that which you intend to label. An examination of your data indicates insufficient numbers of total patients exposed and an insufficient number receiving rapid infusion rates.**

   Meeting Discussion:
   The Division is concerned that the current safety exposure to the higher dose range at high infusion rates is insufficient. This was underscored by the small 12 patient cohort of open line that had a range of 2 to 26 minutes. This apparent very limited adherence to the target exposure rate was clarified by the sponsor

who indicated that approximately 80% of the subjects received the infusion at the target rate of 2 to 5 minutes. Although the achievement of target infusion rate was better than implied by the 2 to 26 minute range, the safety pool in this range is still not robust. The Division also requests additional safety data for dosages higher than the currently labeled oral dose upper limit of 1600mg. Overall the Division assessment is that an additional 50 patients are necessary for the safety database but will review the requests made of other sponsors that have recently developed IV formulations.

Post meeting comments: We have analyzed the data bases for two recently approved IV formulations. In those cases total exposures varied from 117 to 199 with approximately 15% to 38% of patients receiving higher than labeled infusion rates and about 38% receiving a higher than labeled dose. These infusions contained only the studied drug. As your solubilized carbamazepine formulation contains an additional component, which has its own potential toxicity, we belive that you should model your program to at least cover the high end of aforementioned developmental programs. In that case you should have approximately 200 patients exposed with approximately 40% receiving higher infusion rates and dosages. Of course these higher rates and dosages should be only performed once lower rates and dosages prove to be safe and should be slowly advanced depending on prior safety experience.

2. **Study OV-1015 amendment # 4 increased allowable study enrollment to 120, however the meeting document page 51 indicates that only 98 enrolled. What accounts for the divergence between the allowable and actual enrollment?**

   There was no discussion of this comment at the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73686	GI-1	LUNDBECK INC	CARBAMAZEPINE IV
IND-73686	GI-1	LUNDBECK INC	CARBAMAZEPINE IV

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/s/

RUSSELL G KATZ
09/22/2009

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 30, 2005
Application: pIND 73,686, IV Carbamazepine
Indication: Epilepsy
Type of Meeting: face-to-face
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Courtney Calder, Pharm.D.

FDA Attendees:
Russell Katz, M.D., Division Director
John Feeney, M.D., Team Leader
Andrew Sostek, M.D., Medical Officer
Lois Freed, PhD., Supervisory Pharm/Tox
Courtney Calder, Pharm.D.., Project Manager
Martha Heimann, PhD, Chem. Team Leader
Ramana Uppoor, PhD, Biopharm Team Leader
Sally Yasuda, Pharm.D., MS,Biopharm Reviewer

Ovation Attendees:
Dr. (b) (4), Consultant
Dr. Stephen Collins, VP, Clnical Affairs
Tim Cunniff, VP, Reg. Affairs
Dr. Aravind Krishma, Director Manufacturing/Devel.
Dr. Gerold Mosher, Product Devel.
Kathy Patterson, Associate Director, Reg. Affairs
Dr. Reid Patterson, Pre-clinical consultant
Dr. Mike Rice, VP, Manuf. Devel.
Jerey Rybicki, Senior Associate, Reg. Affairs
Dr. Katherine Tracy, VP, Clinical Research
Navid Varjavandi, Associate Director, Clinical Affairs Operations

This was a pre-IND meeting to discuss the development of IV Carbamazepine.
Discussion Points: Below are the comments from the meeting from each discipline.

Nonclinical

1. In form, the sponsor's plan appears adequate to support the initial clinical trial proposed; however, a final determination of adequacy will be based on review of the data submitted.

2. One-month intravenous toxicity studies in rodent and nonrodent and an embryofetal development study in one species (with justification for the species selected) would be needed for this product. These studies would not be needed prior to acute-dose clinical trials.

3. There is a concern regarding the use of SBECD in the pediatric population. The sponsor should provide any available information that might address this concern.

Clinical

1. The division noted that, although developed for IV replacement therapy, similar IV products are often used off-label at higher doses and higher infusion rates. Therefore, the sponsor should gather some safety experience at higher doses/higher infusion rates during development.

2. The sponsor asked if a waiver for pediatric studies of the IV formulation under the age of 2 years would be granted. Dr.Katz noted that PREA would allow the division to ask for any studies deemed important for pediatric use, regardless of currently labeled indications for oral carbamazepine. Therefore, the sponsor would need to make a case for not doing studies in pediatric patients under age 2 years and the division would consider the arguments made in deciding whether to grant a waiver/deferral of further pediatric studies.

OCPB Comments on Study Design:

1) OCPB recommends a single dose BE study prior to the proposed steady state study in adults. However, the sponsor argued that this is not necessary given the induction characteristics of carbamazepine and also the expected use of IV carbamazepine as an alternative for patients in whom continued use of oral carbamazepine is temporarily not feasible. On discussion with the sponsor , OCPB agrees that the proposed steady state study in adult patients (with the proposed IV
formulation) is acceptable, with inclusion of the full PK profile from the oral CBZ as well as from the IV infusion after the first dose and at steady state, and provided that the range of oral doses is covered (could bracket with high and low doses). The study should be powered to show bioequivalence, based on the variability in the PK data.

2) The sponsor stated limitations to performing a steady state study in the pediatric population. Therefore, the proposed pediatric study would be acceptable to characterize the PK after IV administration in pediatrics, provided that the stable-labeled proposed formulation is used. The PK after the single IV dose in pediatrics (at steady state on oral carbamazepine) should be compared to that after the first IV dose in adults. Also, the sponsor should provide justification that the stable label does not have an impact on the PK.

3) The Division also suggested that the sponsor evaluate the effect of faster infusion rates.

4) To determine whether the patients are at steady state with oral CBZ prior to randomization, 3 trough concentrations should be collected.

5) OCPB will be interested in evaluating the PK profiles of parent and metabolite after oral and IV administration to determine whether the route of administration has an effect on the P450-mediated metabolism of CBZ.

6) In the pediatric study, the sponsor should include a sufficient number of subjects to adequately characterize the PK of IV CBZ across the age range of children including the brackets of 2-6 y.o., 6-12 y.o., and > 12 y.o., with an approximately equal distribution of gender in each age bracket, and with ages reasonably distributed within each bracket.

Minutes Preparer: _____
Courtney Calder, Pharm.D.

Chair Concurrence: _____
Russell Katz, M.D.

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/s/

Russell Katz

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